Sjögren’s syndrome - immunological mechanisms, clinical presentation and management

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Abbreviations

AIB - autoimun bolest
ACR - American College of Rheumatology
AECG - American European Consensus Group
AIDS - acquired immune deficiency syndrome
ANA - antinuclear antibody
ARDS - acute respiratory distress syndrome
BAFF - B cell activating factor
BLK - B Lymphoid Kinase
BTK - Bruton's tyrosine kinase
CA6 - carbonic anhydrase 6
CNS - central nervous system
COVID-19 - Coronavirus disease - 19
DC - Dendritic cells
DHEA - dehydroepiandrosterone
DMARD - disease-modifying anti-rheumatic drug
DNA - Deoxyribonucleic acid
EULAR - European League Against Rheumatism
EBV - Epstein-Barr virus
GVHD - graft versus host disease
HCV - hepatitis C virus
HHV6 - human herpesvirus 6
HIV - human immunodeficiency virus
HLA - human leukocyte antigen
IFN - interferon
IL - interleukin
IM - intramuscular
MALT - mucosa-associated lymphoid tissue
miRNA - microRNA
MRI - magnetic resonance imaging
NFkB - nuclear factor kappa-light-chain-enhancer of activated B cells
PSP - parotid secretory protein
pSS - primary Sjögren’s Syndrome
RA - rheumatoid arthritis
RNA - ribonucleic acid
SGECs - salivary gland epithelial cells
SLE - systemic lupus erythematosus
SP-1 - salivary protein-1
SS - Sjögren’s Syndrome
sSS - secondary Sjögren’s Syndrome
SSRI - selective serotonin reuptake inhibitor
TCA - tricyclic antidepressant
Tfh - follicular T helper cells
Th cells - T helper cells
TLR - toll-like receptor
TNF - tumor necrosis factor
TSAs - tissue-specific autoantibodies

Contents

1. Summary

Sjögren Syndrome (SS) is a chronic systemic autoimmune disease of unknown etiology, primarily affecting the exocrine glands. Clinically, this manifests as decreased secretion of lacrimal glands and salivary glands with a feeling of dry eyes (xerophthalmia) and a dry oral mucosa (xerostomia), as well as dryness of the mucous membranes of the respiratory, gastrointestinal, and urogenital systems. In addition to the glandular manifestations, extra glandular manifestations can also occur. These involve the musculoskeletal system, the interstitium of the lungs, internal organs, and the peripheral and central nervous systems. Primarily affecting women in their 5th and 6th decades of life, Sjögren's syndrome is the most common autoimmune disease after rheumatoid arthritis (RA). The Immunopathogenesis of SS includes a dysregulation in the interaction of endogenous and exogenous factors at systemic and local levels in genetically predisposed individuals. Sjögren's syndrome may manifest as primary Sjögrens syndrome (pSS) or secondary if associated with other autoimmune diseases. The diagnostic procedure is based on the diagnostic criteria established by the American-European Consensus Group in 2002, which have been revised several times since then and include a variety of diagnostic tests, including the Schirmer test, serology, biopsy, and imaging. In the past, the treatment of Sjögren's syndrome has mainly focused on relieving the symptoms and suppressing the immune system, more recently the subject of research has been immunotherapy, biological therapy, and stem cell therapy. As an alternative therapy, Chinese medicine has shown a positive effect on patients with Sjögren Syndrome.

Keywords: Sjögren Syndrome, sicca symptoms, autoimmune disease, immunity

2. Sazetak

Sjoegrenov sindrom (SS) je kronična sustavna autoimuna bolest (AIB) nepoznate etiologije koja primarno zahvaća egzokrine žlijezde. Klinicki dominira smanjena sekrecija suznih žlijezda i žlijezda slinovnica s osjecajem suhoće očiju (kseroftalmija) i sluznice usne šupljine (kserostomija) ali i suhoca sluznice respiratornog, gastrointestinalnog i urogenitalnog sustava. Sjogrenov sindrom se očituje glandularnim ili extraglanularnim oblikom sa zahvaćanjrm koštano-mišićnog sustava, intersticija pluća, unutrašnjih organa, perifernog i središnjeg živčanog sustava. Primarno oboljevanu žene u 5. i 6. desetljeću života, a nakon reumatoidnog artritisa (RA) najčešća je autoimuna bolest. U imunopatogenezi dolazi do poremećene regulacije u interakciji endogenih i egzogenih čimbenika. na sistemskoj i lokalnoj razini u genetski predisponiranih osoba. Sjoegrenov sindrom se može očitovati kao primarni Sjoegrenov sindrom (pSS),ili sekundarni ako je pridružen drugim AIB Imunohistološka i serološka obilježja bolesti se očituju limfocitnom infiltracij žlijezda slinovnica sa stvaranjem ektopičnih zametnih centara, kao i prisutnost Anti-Ro i Anti-La autoantitijela u serumu. Postupak dijagnostike temelji se na dijagnostickim kriterijima Američko-europske skupina za konsenzusm 2002. godine, a koje su od tada nekoliko puta revidirane, a uključuje mnoštvo dijagnostičkih testova, poput Schirmerovog testa, serologije, biopsije i snimanja. U prošlosti se liječenje Sjögrenovog sindroma uglavnom fokusiralo na ublažavanje simptoma i supresiju imunološkog sustava. U zadnje vrijeme, predmet istraživanja je imunoterapija, biološka terapija i terapija s matičnim stanicama, kao alternativna terapija temeljema na drevnoj kineskoj medicini za koju je opaženo Povoljan učinak na simptome u bolesnika sa Sjögrenovim sindromom.

Ključne riječi: Sjögrenov sindrom, simptomi sicce, autoimuna bolest, imunitet

3. Introduction

Sjögren's syndrome is a systemic autoimmune disorder, predominantly affecting middle-aged women (the female to male ratio is 9:1), which typically causes a dysfunction of secretory glands (1,2). The most common symptoms experienced are the so-called sicca symptoms, which manifest as dry mouth and eyes, but the disease also expresses itself in the dryness of other mucosal surfaces such as the pharynx, larynx, nose, and vagina. In addition to that, other organ systems like the skin, liver, CNS, the nephro-urological system, and the hematological system can be affected. Even with the expression of the typical sicca symptoms, this disease often goes underdiagnosed or misdiagnosed by general practitioners. The cause of Sjögren's syndrome remains unknown but a combination of genetic and environmental factors is suspected to play a role in the development of the disease. Whenever the sicca symptoms appear in a person without any other autoimmune diseases, it is called primary Sjögren's syndrome (pSS). The secondary form of Sjögren's syndrome (sSS) is associated with other autoimmune diseases such as scleroderma, systemic lupus erythematosus, or rheumatoid arthritis (1).

4. Epidemiology

Several studies have proven that Sjögren Syndrome (SS) occurs mainly in perimenopausal women, peeking around the age of 51-65, with a female to male ratio close to 10:1 (3,4). In men, SS occurs less often and usually starts at a later age, aged 65 and older (3). The incidence of pSS is 3 to 11 per 100,000 people, while the prevalence lies between 0.01% and 0.72%. (4). The highest prevalence of SS is found in Europe (5). The phenotypic expression of SS is also found to differ between men and women, with men more often presenting with severe ocular involvement but less severe systemic involvement compared to women (6,7). Unfortunately, there is very little research done, examining the impact race or ethnicity have

on the development of SS, though one study done on the population of the Greater Paris area suggests that there is a significantly higher prevalence of primary SS among people with a non-European background in comparison to people with European background (8).

5. Immunopathology

The dysfunction of exocrine glands in SS is associated with the characteristic histologic finding of periductal infiltration of lymphocytic cells, mainly consisting of activated T (70-80%) and B cells (20-25%), Dendritic cells (DC), and Macrophages (2,9), as well as B cell hyperactivity leading to hypergammaglobulinemia, autoantibodies (Anti-Ro and Anti-LA and ANA) and the consumption of complement (2). Despite the extensive research conducted in this field, the exact etiology of SS has not been found yet, though it is suspected that epithelial cells, especially the salivary gland epithelial cells (SGECs), play an important role in the pathogenesis of the disease (2,10).

Immune activation in epithelial cells

According to recent research, the SGECs seem to be a starting point in the development of SS. Intrinsic epithelial activation and overexpression of HLA class II, especially HLA-DR, appear to be preceding the process of lymphocytic infiltration. SGECs produce a multitude of cytokines that play an important role in innate as well as adaptive immunity. One example of that would be the production of cytokines (IL-6, IL-7, IL-18, IL-22) that play a role in Th1, Th17, and T follicular helper cell response as well as B cell stimulation (10). Research suggests that SGECs in patients with SS produce more than 40 times the amount of IL-1 alpha, TNF-alpha, and IL-6 mRNA in comparison to SGECs in patients without SS (11). In addition to this, they produce B cell activating factor (BAFF), which plays a big role in the maturation, class switching, survival, and proliferation of B cells, especially in the later

stages of SS. Another factor that might play a role in the development of SS is the production of several chemokines (CXCL13, CCL17, CCL19, CCL22) that leads to DC infiltration (10). An additional element that may be connected to the etiology of SS is the higher expression of Toll-like receptors (TLR-2, TLR-3, and TLR-4 as well as TLR-7 and TLR-9) in SGECs in patients with SS in comparison to SGECs in the control group, which indicates the induction of an innate immune response by SGECs (12,13,14). The TLR signaling pathway has proven to be involved in the production of a multitude of proinflammatory cytokines as well as the upregulation and expression of various adhesion and costimulatory molecules which links innate immune reactions to the activation of the adaptive immune system (13). Previous research suggests that TLR molecules play a role in the pathogenesis of other autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and autoimmune pancreatitis, which further indicates that TLR molecules might also play a role in the pathogenesis of SS (12).

SGECs in patients with SS are also suspected to have a faulty feedback regulation of NFkB, which then again leads to increased production of inflammatory cytokines. Research on mice models with homozygous knock-in kB enhancers suggests that the increased NFkB activity plays a role in higher serum levels of IL-1 alpha, IL-17 and TNF alpha, anti-Ro/SS-A, and anti-La/SS-B antibodies as well as the lymphocytic infiltration of salivary and lacrimal glands (15). Ro and La antigens are released by SGECs upon apoptosis, mediated by the Fas-Fas ligand pathway, and subsequently presented to T cells (16). Following this, anti-Ro and anti-La antibodies are produced in the ectopic germinal centers located in the exocrine glands (17). All these processes starting in the SGECs lead to inflammation of the salivary glands, proliferation of lymphocytes, and formation of ectopic germinal centers.

Lymphocytes

As previously mentioned, the typical histopathological picture in SS is that of periductal infiltrating lymphocytes, mainly T cells and B cells. Infiltrating Th1 cells produce IFN gamma, which in turn leads to the differentiation of CD4+ lymphocytes into Th1 cells (10). Th17 cells also seem to play an important role in the pathogenesis of SS. Increased expression of IL-17 in the blood, as well as expression of its mRNA in salivary gland biopsies, has been found in patients with SS (18). In conjunction with IL-22, which is another cytokine in the Th17 pathway, IL-17 can cause a severe inflammatory response and recent studies have also linked elevated serum levels of IL-22 in SS patients to hyposalivation and elevated levels of Anti-Ro and Anti-La antibodies (19,20).

Follicular T helper cells (Tfh), as their name suggests, are important for the formation of lymphoid follicles and therefore the development of ectopic germinal centers in SS. They secrete the cytokine IL-21 which plays a role in the maturation of B cells and the formation of the previously mentioned germinal centers. T helper cells are induced to differentiate into Tfh by IL-6, secreted by SGECs (10). High levels of T regulatory cells are found in the salivary glands in SS. One theory explaining this finding is that T regulatory cells are responsible for the regulation of immune responses and are therefore trying to oppose the inflammatory reaction caused by other immune cells (21).

Another feature of SS is B cell hyperactivity, which manifests as autoantibody positivity, serum polyclonal hypergammaglobulinemia, cryoglobulinemia, and occasionally ectopic germinal center formation as well as a higher chance of developing B cell lymphoma later on in the course of the disease. The amount of B cells infiltrating the exocrine glands increases with the progression of the disease. BAFF levels have been proven to be elevated in SS patients, and in contrast to healthy persons, in SS patients B cells, T cells, and SGECs are able to secrete BAFF. BAFF is also suspected to play a role in the formation of ectopic

germinal centers and to be one of the reasons for B cell hyperactivity (10,22). Ectopic germinal centers in the salivary glands can be found in 10-30% of SS patients and B cells producing autoantibodies are found primarily in the margins of these germinal centers (22). These germinal centers are not only the main site of increased apoptotic activity but also a predisposing factor for the development of lymphoma (10). CXCL13, produced by DCs, stromal cells, and some T cells, is a chemokine that directs B cell chemotaxis and was found to be elevated in the serum and saliva of SS patients. It is thought to contribute to the recruitment of lymphocytes to the salivary glands and could therefore be used as a biomarker in SS (23).

New biomarkers

In recent years the search for new biomarkers that can be used for early diagnosis of SS has been a focus in the SS research. The earlier SS is diagnosed, the better the treatment outcome. Therefore it is very important to develop methods that are able to detect SS as early as possible. Several tissue-specific autoantibodies (TSAs), such as anti parotid secretion protein (anti-PSP), anti carbonic anhydrase 6 (anti-CA6), and anti salivary protein-1 (anti-SP-1), that are present in the early stages of SS have been identified. These TSAs can be found earlier than the classic antibodies used for the diagnosis of SS. Out of these newly discovered TSAs, especially SP-1 has been found to be associated with SS. Also, anti-CA6 is suspected to be prevalent in patients with xerophthalmia and is thought to be associated with more severe disease and younger age (14).

Another approach that has recently been taken is the search for biomarkers not only in the blood but also in the saliva and tears of patients. The tear proteins LACTO and LIPOC-1 have recently been found to be useful in the diagnosis of SS. Also, the concentration of SS100A8/A9 in the saliva is of interest since it has been found to differ in different groups of

SS patients, depending on their risk of developing lymphoma (14). Even though these newly found biomarkers seem to be promising they have to be further evaluated to prove their usefulness in the early diagnosis of SS.

6. Genetic, Epigenetic and Environmental factors

Genetics is thought to contribute to the development of SS. Research suggests that in up to 38% of patients with SS at least one first-degree relative also has an autoimmune disease. Some of the more common autoimmune diseases clustering in families of patients with SS are autoimmune thyroid disease, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (24,25). Both HLA and non-HLA genes are associated with the development of autoimmune diseases. In SS patients with Anti-Ro and Anti-La antibodies, HLA-DQ and HLA-DR have a strong association with the development of disease (26). Other gene polymorphisms associated with SS include BLK, STAT4, TNIP1, IL-12A, IRF5, and CXCR5. Some of these mutations are not in the DNA coding regions and are suspected to act on the gene expression indirectly via epigenetic modification. The epigenetic mechanisms altered in SS include DNA methylation in epithelial cells as well as abnormal chromatin positioning which is linked to the production of autoantibodies as well as abnormal expression of miRNA (14). Since SS is mostly affecting females, the connection of epigenetic methylation of the X chromosome to the pathogenesis of the disease has also been the subject of research. So far, 58 X chromosome genes were found to be upregulated in SS (14).

Another aspect connected to the female predominance has been the presumption that sex hormones may be involved in the pathogenesis of SS. Surprisingly though, several studies suggest that estrogen has a protective effect, which might be the reason why the disease mostly occurs perimenopausal when the levels of estrogen in the body decline (27)

Viral infections, especially infections with the Ebstein-Barr virus (EBV), but also other members of the family of herpesviridae, such as human herpesvirus 6 (HHV6), are thought to be an important environmental factor in the pathogenesis of SS. The viruses damage epithelial cells and stimulate an immune reaction and are therefore thought to trigger the processes involved in the pathogenesis of SS. In addition to this, high levels of EBV-antibodies, as well as high levels of antibodies specific for HHV6 have been found in the serum of SS patients (4,28).

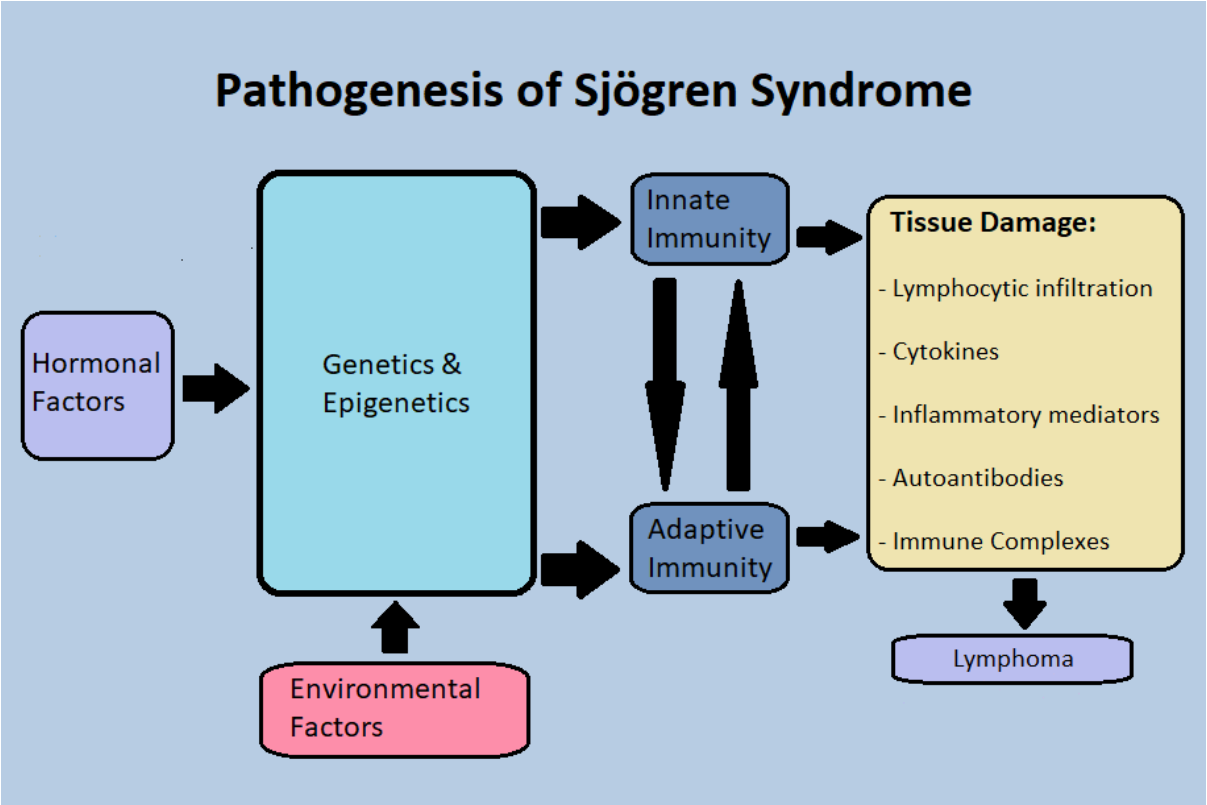

Figure1.: pathogenesis of SS

7. Clinical picture

Sicca Symptoms

The pathognomonic symptoms of SS are the so-called sicca symptoms, namely dryness of the mouth (xerostomia) and dryness of the eyes (xerophthalmia). These symptoms occur in

85-95% of patients diagnosed with SS and approximately 30% of SS patients develop episodic inflammatory swelling of the parotid and submandibular glands (1,14).

As already mentioned, xerostomia manifests as dryness of the mouth due to the alteration of function and destruction of salivary glands and the resulting decrease of saliva production (1,29). This lack of saliva also elicits other problems such as dysphagia, soreness of the mouth and adhesion of food to the mucosa, problems with eating and speaking, infections, and tooth decay. Oral signs of SS include angular cheilitis and an erythematous, depapillated, or lobulated tongue as well as a dry and sticky oral mucosa (1,4). Patients suffering from xerostomia often report the urge to drink a lot, especially while eating, to combat their dry mouth and to help relieve their dysphagia (29). Dental caries is also a common finding in SS, usually found in the cervical region as well as on the smooth surface of the teeth (4).

Xerophthalmia due to diminished secretion of tears in combination with increased tear evaporation causes an itchy, burning, and gritty feeling of the eye and can lead to photosensitivity, soreness of the eye, and reduced visual acuity (1,14). More recently, it was discovered that the destruction and dysfunction of the meibomian glands is also a factor in the development of xerophthalmia in SS (14). The eyes of SS patients usually look red and irritated and might show dilated conjunctival blood vessels (4). Later on in the course of the disease patients with SS develop keratoconjunctivitis sicca, which is the chronic irritation and damage to the conjunctival epithelium, and corneal ulcers (1,14). All of this is a predisposition for the development of severe eye infections and permanent damage to the eyes that can ultimately lead to severe visual impairment (1).

Additional sicca symptoms include dry skin, hoarseness, dry cough, and dyspareunia in women due to dryness of vaginal mucosa (1).

Extra glandular manifestations

Besides these sicca symptoms, approximately 25% of patients with SS also suffer from extra glandular manifestations of the disease (30,31,32). As in many other autoimmune diseases, any organ system can be involved in SS, but the most common extra glandular manifestations occur in the lungs, blood, gastrointestinal system, musculoskeletal system, and nervous system (30). Additionally, many SS patients also suffer from general symptoms like fatigue, fever, and weight loss as well as Raynaud's phenomenon and vasculitic rashes (33).

Pulmonary involvement belongs to the more common extra glandular manifestations (34). It has been reported in up to 20% of patients suffering from SS. Symptoms of the pulmonary manifestations are very broad and reach from dyspnea and chronic cough to chest pain. In a small group of SS patients, pulmonary symptoms may be the first manifestation of the disease. Both, the airways (small and large) as well as the lung parenchyma may be affected by SS. Airway diseases connected to SS include bronchiolitis, hyperreactive airways, and bronchiectasis. Interstitial lung diseases such as nonspecific interstitial pneumonitis may also be associated with SS (32,34). Other pulmonary manifestations of SS include cystic lung disease, pulmonary lymphoma, and lymphocytic interstitial pneumonitis (34).

Hematologic manifestations of SS include most commonly the anemia of chronic disease, lymphopenia as well as leukopenia. Less commonly, hemolytic anemia, thrombocytopenia, autoimmune neutropenia, and agranulocytosis are part of SS. Cryoglobulinemia might occur as well, sometimes accompanied by vasculitis (30).

Non-Hodgkin's B-cell Lymphoma is without question one of the most dangerous complications of SS. It occurs in 5-7% of patients with SS, most commonly within 10 years of the diagnosis. It often presents with sustained swelling of the salivary glands, especially

the parotid gland, but can also arise at nodal or even extranodal sites like the spleen, liver, lungs, or stomach (30). The parotid gland swelling of lymphoma, compared to benign parotid swelling is usually unilateral as well as fixed and hard. MRI and ultrasonography can be used to differentiate between benign parotid enlargement and lymphoma (4). The most common types of lymphoma occurring with SS are the marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue (MALT) as well as diffuse large B cell lymphoma (30). The increased risk of developing lymphoma in SS is suspected to be connected to the activation and chronic stimulation of polyclonal B cells as well as the persistent exposure to autoantigens and immune activation. The presence of ectopic germinal centers within the exocrine glands as well as cryoglobulinemia and chronic glandular swelling as a result of heavy MALT involvement is seen as a predictive risk factor for the development of lymphoma in SS (4,14). More recently novel biomarkers predicting lymphoma development have been the subject of research. Low levels of miR200b-5p, as well as high levels of thymic stromal lymphopoietin in the serum, were found to be promising predictors of lymphoma development (32).

The gastrointestinal symptoms of SS have a very wide spectrum. They may include reflux, dyspepsia, and chronic constipation in addition to the previously described xerostomia and dysphagia. These problems may be directly caused by the decreased production of saliva as well as by motility problems. Since SS may also be associated with other autoimmune diseases, autoimmune pancreatitis may occur as well as concurrent celiac disease with diarrhea (30).

Musculoskeletal symptoms manifest mainly with inflammatory muscle and joint pain as well as synovitis in up to 35% of patients. Usually, these symptoms occur in multiple places (polyarticular) but oligoarticular and monoarticular symptoms have also been reported. The

most commonly affected joints are the knee, wrist, and small joints of the hand. In most cases, the arthritis accompanying SS is non-erosive and does not deform the joints (30).

Neurological manifestations are reported in 8-49% of patients with SS. The symptoms range from multiple sclerosis-like CNS involvement to psychiatric disorders and entrapment neuropathies. The most commonly manifesting symptoms of peripheral nerve disease in SS are distal sensory and sensorimotor neuropathies. Sensory neuropathies include trigeminal neuropathy and dorsal root ganglionitis and may manifest with severe neuropathic, usually burning or lancinating pain. Sensorimotor neuropathies may manifest as mononeuritis multiplex or sensorimotor polyneuropathy. The CNS involvement includes problems with memory, psychiatric disorders like depression, encephalitis, aseptic meningitis, and many more. These CNS symptoms seem to be caused by immunologically mediated small vessel vasculopathy and vasculitis (35).

Interstitial nephritis causing renal tubular acidosis, hypokalemia, and nephrogenic diabetes insipidus as well as myocardial disease and pericarditis do also belong to the possible extra glandular complications of SS (33). Around 20% of patients with primary SS develop some sort of autoimmune thyroiditis, mostly Hashimoto's but also Graves' disease, at some point. More than 50% of SS patients are also diagnosed with subclinical hypothyroidism (31).

Several studies have shown that SS patients also have a higher likelihood of developing cardiovascular risk factors such as hyperlipidemia and hypertension. In addition to this SS patients have also been found to have a higher risk of developing aortic dissection and aneurysms (14). During pregnancy in Anti-Ro/Anti-La positive women, the autoantibodies can cross the placenta and cause congenital heart block in the fetus (14,31)

8. COVID-19 in Sjögren syndrome patients

Since the Covid-19 pandemic emerged at the beginning of 2020, many doctors and scientists have researched the effects this virus has on the human body. One big concern was and still is, how the virus affects people who already have pre-existing illnesses, especially with autoimmune illnesses such as SS. A retrospective study conducted on 51 COVID-19 positive patients with SS came to the result that poor outcomes were higher for patients with pSS that also have other comorbidities such as chronic pulmonary diseases, cardiovascular diseases, obesity, or diabetes. This suggests that the development of complications is rather related to the comorbidities than to the SS itself. Other than this, patients with primary SS seem to be affected by COVID-19 similarly to the general population (36). Another scientific paper, a case report, describes the case of an 85-year-old man with SS that was tested positive for COVID-19. This patient had several risk factors for a poor outcome of his infection such as old age, hypertension, and corticosteroid use. In the course of the disease, he developed ARDS and was treated and cured with a combination of ciclesonide, favipiravir, corticosteroids, and the off-label use of tocilizumab. In this case, tocilizumab, an IL-6 receptor binding monoclonal antibody that reduces inflammatory reaction and is predominantly used in the treatment of RA and systemic juvenile idiopathic arthritis, was thought to have a positive effect on the patient's respiratory failure. This implies that the utilization of tocilizumab and other IL-6 receptor blockers could be of use in the treatment of COVID-19 and should be subject to bigger research studies (37).

9. Secondary Sjögren syndrome

Secondary SS occurs in association with other autoimmune diseases, such as RA, systemic sclerosis, SLE, or hypothyroidism (38,31). Up to 30% of SS patients are considered to have the secondary form of the disease. It is considered secondary even if SS is diagnosed years

earlier than the other autoimmune disease. Some patients with sSS are diagnosed with several different autoimmune diseases. (31).

10. Differential Diagnoses

Before diagnosing a patient with SS, other causes for the symptoms experienced should be excluded. One differential diagnosis for dry eyes could be the so-called dry eye syndrome which occurs either due to decreased tear production or increased evaporation of tears. Decreased production of tears could be caused by a dysfunction of the nervous cells and receptors monitoring and regulating the production of tears. Increased evaporation can be a consequence of multiple causes. These causes could be intrinsic, such as eyelid disorders and incomplete blinking, or extrinsic, such as contact lens wear, vitamin A deficiency, or ocular surface disease (39). Some other differential diagnoses that should be considered before diagnosing SS are age-related sicca symptoms, lymphoma, GVHD, sarcoidosis, head and neck radiation, and chronic viral infections (HCV, HIV). Certain medications can also produce sicca symptoms and should be considered in the diagnostic process. Examples are anticholinergic drugs, SSRIs, TCAs, benzodiazepines, antihistamines, opioids, beta-blockers, diuretics, retinoids, and many more (33).

11. Diagnosis

The diagnosis of SS is based on the criteria introduced by the American-European Consensus Group (AECG) in 2002, shown in table 1 (40). The presence of any four out of the six criteria mentioned is suggestive of primary SS as long as either serology or histopathology is positive. The diagnosis of primary SS is also indicated if three out of the four objective criteria are present. For the diagnosis of secondary SS, patients must have at least one other potentially associated autoimmune disease combined with the presence of at least one ocular

and oral symptom, as well as any two of the objective criteria. Exclusion criteria for the diagnosis of SS include previous head and neck radiation, HCV infection, AIDS, preexisting lymphoma, GVHD, sarcoidosis, and the use of anticholinergic drugs (40). In 2012 the American College of Rheumatology (ACR) developed new criteria for pSS, seen in table 1, in an attempt to make the classification criteria more objective (41).

In 2016 the ACR and the European League Against Rheumatism (EULAR) have revised the classification criteria and published new ones, a combination of the ACR and AECG criteria (table 2.). With the ACR/EULAR criteria, a patient that has >4 points is considered to have pSS (41).

Table 1.: Diagnostic criteria

Revised international classification criteria for SS according to the American-European consensus group (2002)	**ACR criteria from 2012**
Ocular symptoms: a positive response to at least one of the following questions: ● Have you had daily, persistent, troublesome dry eyes for more than 3 months? ● Do you have a recurrent sensation of sand or gravel in the eyes? ● Do you use tear substitutes more than 3 times a day?	**Ocular symptoms**: not included
Oral symptoms: a positive response to at least one of the following questions: ● Have you had a daily feeling of dry mouth for more than 3 months? ● Have you had recurrently or persistently swollen salivary glands as an adult? ● Do you frequently drink liquids to aid in swallowing dry food?	**Oral symptoms**: not included
Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: ● Schirmer's test, performed without	**Ocular signs:** Keratoconjunctivitis sicca with ocular staining score ≥ 3 (bengal red or lissamine green staining)

anesthesia (< 5mm in 5 minutes) ● Rose bengal score or other ocular dry score (> 4 according to Bijsterveld's scoring system)	
Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue	**Histopathology**: Lower lip gland biopsy showing focal lymphocyte salivary gland inflammation ≥ 1 lymphocyte foci/ 4 mm² (at least 50 lymphocyte aggregation in 4 mm²)
Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: ● Unstimulated whole salivary flow (<1.5 ml in 15 minutes) ● Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts ● Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer	**Salivary gland involvement**: not included
Autoantibodies: Presence in the serum of the following autoantibodies: ● Antibodies to Ro(SSA) or La(SSB) antigens, or both	**Autoantibodies**: Positive serum anti−Ro and/or anti−La (or positive rheumatoid factor and ANA titer ≥ 1:320)

According to Vitali C, et al., 2002; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002 Jun;61(6):554-8 and Chen X, Wu H, Wei W. Advances in the diagnosis and treatment of Sjogren's syndrome. Clin Rheumatol. 2018 Jul;37(7):1743-1749. doi: 10.1007/s10067-018-4153-8. Epub 2018 May 26. PMID: 29804149.

Table 2.: ACR/EULAR criteria from 2016

Criteria	Weight
Labial salivary gland with focal lymphocytic sialadenitis and focus score of >1 foci/4 mm	3
Anti-Ro positive	3
Ocular staining score > 5 in at least one eye	1
Schirmer's test < 5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate < 0.1 ml/min	1

Chen X, Wu H, Wei W. Advances in the diagnosis and treatment of Sjogren's syndrome. Clin Rheumatol. 2018 Jul;37(7):1743-1749. doi: 10.1007/s10067-018-4153-8. Epub 2018 May 26. PMID: 29804149.

According to the American-European Consensus Group criteria, the patients are first given six questions to answer, concerning oral and ocular symptoms. After this, the objective criteria are assessed using different tests. The Schirmer's test is used to diagnose keratoconjunctivitis sicca. In this test, a piece of sterile Schirmer's test filter paper is inserted under the lateral third of the patient's lower lid and left there for 5 minutes with the patient's eyes shut. It is considered positive if after these 5 minutes less than 5mm of paper is wet. Damage to the conjunctival epithelium can be evaluated using ocular dye tests. The Rose Bengal scoring is used to evaluate the intensity of staining of the cornea and conjunctiva (33). It is one of the most often used tests for the evaluation of damage to the ocular surface epithelium. Fluorescein dye is used in addition to the previously mentioned tests to assess the tear break-up time (33).

To measure saliva production, the Saxon test can be used. In this test, the patient chews for 2 minutes on a twice folded pad with the measurements 7,5 x 7,5 cm. After this, the saliva-soaked pad is weighed and the difference in weight before and after the test equals the amount of saliva the patient has produced. More than 2,75g of saliva produced in 2 minutes is considered normal, everything below this number is considered pathological (29).

Serology and laboratory tests are another step in the diagnosis of SS. Many patients with SS demonstrate abnormalities including a high erythrocyte sedimentation rate, hypergammaglobulinemia, cytopenias, and positive autoantibodies. The presence of Anti-Ro and Anti-La autoantibodies is part of the aforementioned classification criteria (33). Approximately 50-60% of patients with SS are positive for Anti-Ro, but Anti-Ro antibodies are quite unspecific, they also occur in approximately 50% of SLE patients. Anti-La antibodies are considered to be more specific, but can only be found in 25-30% of patients with SS (29). Rheumatoid factor and ANA are also found positive in many SS patients (33).

Another major diagnostic tool for SS is the salivary gland biopsy. It is commonly done in patients with serology negative for Anti-La but with persisting suspicion of SS (29). In this procedure, approximately five minor salivary glands are removed surgically from the lower lip, to be examined histopathologically. The main histopathologic finding in the biopsied salivary glands is the periductal lymphocytic infiltration. More than 50 lymphocytes per 4mm² are called focus and two or more foci are considered to be a focal lymphocytic sialadenitis (33,40).

In addition to this parotid sialography can be performed. This is a contrast media X-ray study, in which a radiopaque contrast medium is injected into the orifice of the salivary gland to visualize the salivary glands (33,42). If the parotid sialography demonstrates diffuse sialectasis, which is the diffuse, cystic dilation of the salivary gland ducts, the diagnosis of SS is very likely. Scintigraphy using radiolabeled tracer material might also be used as a noninvasive alternative diagnostic procedure. Additionally, MRI and ultrasound imaging can also be used to demonstrate changes in the salivary glands (33). Salivary gland ultrasonography is used to examine the parotid and submandibular glands for diagnostic and follow-up purposes. With ultrasound, the echogenicity, as well as structural and degenerative

changes, can be visualized. In addition to this, Doppler ultrasonography can be used to show salivary gland vascularity (43).

After being diagnosed with SS, patients are usually followed up by a rheumatologist. Depending on the severity of their symptoms they might only need an annual check-up by their family physician or rheumatologist. For patients with extra glandular symptoms more frequent evaluations by a rheumatologist are recommended. Blood tests are used to monitor their kidney function, thyroid function, cytopenias, and additional urine analysis is used for more information about the renal function. The risk for development of lymphoma has to be assessed regularly in SS patients, this includes the assessment of possible B symptoms like fever and weight loss as well as the examination of lymph nodes and salivary glands for swelling. Another useful tool for the assessment of lymphoma risk is the monitoring of autoantibodies, lactate dehydrogenase, and cryoglobulins. In case of a suspicious lesion being found, imaging and biopsy have to be performed. Regular visits to the dentist and the ophthalmologist are also recommended (33).

12. Treatment

So far, despite extensive research in this field, no definite treatment to stop the progression of or even completely cure SS has been found. Therefore the current treatment methods concentrate mainly on alleviating the symptoms connected to SS and preventing further damage to the organs from occurring. In a more recent approach, immunosuppressive and immunomodulatory drugs are used in an attempt to restore the normal function of the immune system (33). Patients that are at risk for developing lymphoma or systemic complications should be followed-up closely with regular visits to their treating specialist, every 3 to 6 months. For patients with a lower risk of developing complications, yearly

checkups are sufficient (4). Self-care measures and regular exercise is recommended to reduce the fatigue commonly accompanying SS (44).

Treatment of sicca symptoms

Good oral hygiene, regular check-ups at the dentist, and caries prophylaxis with fluoride are essential for the management of the oral symptoms because of the increased risk of dental caries formation and tooth decay (33,45). To help moisten the oral cavity patients can use artificial saliva products, such as mucin, hydroxyethylcellulose, or carboxymethylcellulose, in gel or spray form (31,33). Additionally, sugar-free gum is commonly used to help with the stimulation of saliva production (33). Pharmaceutical agents that can be used to alleviate the sicca symptoms are cholinergic agonists such as pilocarpine or cevimeline, these drugs help stimulate saliva and tear production, but often have adverse effects such as increased urinary frequency, nausea, flushing, and sweating (33,46). More recently interventional sialendoscopy, a minimally invasive endoscopic procedure that allows the visualization of salivary ducts and the treatment of obstruction and inflammation, has been the subject of research. It has been found to reduce the episodes of glandular swelling and improve oral dryness (14). In addition to this, the use of dehydroepiandrosterone (DHEA) to treat sicca symptoms has been the subject of a study and has been found to significantly improve the oral dryness of the patients included in the study (47).

Ocular symptoms such as dry, gritty eyes can be alleviated with the use of artificial tears in the form of ointments or eye drops, to moisten the eyes surface (33). These artificial tears have been found to be effective and safe (46). In addition to topical agents, patients should avoid smoky, windy environments, prolonged reading, and computer use and should protect their eyes with goggles or moisture chambers (31). Topical agents like cyclosporine and corticosteroids can be used to decrease inflammatory reactions. As previously mentioned for

the oral symptoms, cholinergic agonists can be used to increase residual tear production (33). Punctal occlusion is a painless, mechanical procedure used in the treatment of chronically dry eyes. In this procedure, the puncta are blocked with a collagen or silicone plug to prevent the tears from draining and increase the amount of liquid present on the ocular surface (33,48). Drugs that might dry out the eyes additionally such as beta-blockers, diuretics, antihistamines, and TCA's should be avoided if possible (35).

In cases of vaginal dryness, non-hormonal moisturizing agents can be used to alleviate the symptoms, in post-menopausal women local hormone replacement can be used additionally (33).

Table 3.: Treatment of sicca symptoms

Treatment of ocular symptoms	**Treatment of oral symptoms**
Artificial tears in the form of eye drops or ointments Topical agents: ● cyclosporine and corticosteroids	Saliva substitutes in gel or spray form: ● mucin, hydroxyethylcellulose, or carboxymethylcellulose Saliva stimulation: ● sugar-free gum or hard candy
Pharmacological therapy with cholinergic agonists: ● pilocarpine or cevimeline	Pharmacologic therapy with cholinergic agonists: ● pilocarpine or cevimeline
Punctal occlusion with a collagen or silicone plug	Active dental care: ● caries prophylaxis with fluoride Interventional sialendoscopy

Treatment of systemic manifestations

Non-biological therapies. Systemic manifestations of SS are being treated with a multitude of pharmacological agents. The first-line treatment for the rheumatologic manifestations of SS, such as inflammatory arthritis and musculoskeletal pain is hydroxychloroquine, some studies have also found an improvement of ocular symptoms with the hydroxychloroquine treatment.

Oral DMARDs such as methotrexate are also used for the treatment of rheumatologic manifestations if the treatment with hydroxychloroquine is unsuccessful (33,44,47). If neither hydroxychloroquine nor methotrexate by itself is successful in the treatment of rheumatologic manifestations, a combination of both drugs should be considered (44). Corticosteroids are commonly used for systemic flare-ups and significant organ manifestations (33). As in many other autoimmune diseases, corticosteroids can be used in SS to reduce inflammatory reactions. They can also be used in conjunction with hydroxychloroquine and methotrexate in the case of severe musculoskeletal pain (44). These short courses of steroid treatments are given either intramuscularly or orally. Low doses of oral prednisolone are commonly used for persistent constitutional symptoms in patients who do not respond well to other immunosuppressive agents (33). Leflunomide, sulfasalazine, azathioprine, and cyclosporine are additional drugs that may be given in case all aforementioned treatment options for the rheumatologic manifestations of SS fail (44).

Systemic complications such as cytopenias, lung disease, neuropathy, myelopathy, and vasculitis are being treated with cyclophosphamide, if this treatment is unsuccessful then mycophenolate, azathioprine, and methotrexate can be used (29,33).

Biological therapies. More recent studies have been investigating the use of Rituximab for the treatment of ocular symptoms in patients refractory to the previously mentioned treatment options. It may also be considered for the treatment of oral symptoms in patients who still have some residual salivary production and who have notable oral damage despite treatment with the aforementioned treatment options. In addition to this Rituximab may also be used to treat systemic signs and symptoms of SS such as parotid swelling, vasculitis, pulmonary disease, inflammatory arthritis, and neuropathies (44,47). Other biologic drugs such as Etanercept, Infliximab, and Belimumab have also been under investigation as a treatment for

SS (46). New studies are currently investigating the use of new drugs, such as BAFF inhibitors, IF alpha inhibitors, and BTK inhibitors for the treatment of SS (29).

Researching the effectiveness of all of these treatments, biologic and nonbiologic is still an ongoing process and can be quite challenging. To this date, the question of which treatment regimen is the best for SS is still up for debate. Many patients that are being included in the trial studies have already advanced in the disease process and have developed fibrosis of the exocrine glands. This fibrosis makes some of the symptoms the patients are experiencing impossible to reverse. In addition to this, many studies researching the drugs are conducted over a rather short period of time and include only a small number of patients (47).

Table 4.: Treatment of systemic manifestations

Non-biological therapies	**Biological therapies**
Hydroxychloroquine: ● first-line treatment for rheumatological manifestations	**Rituximab**: ● treatment of ocular symptoms in patients refractory to other treatment ● may also be considered for the treatment of oral symptoms in patients who still have some residual salivary production and have notable oral damage. ● may also be used to treat systemic signs and symptoms of SS such as parotid swelling, vasculitis, pulmonary disease, inflammatory arthritis, and neuropathies
Oral DMARDs (methotrexate): ● used for rheumatological manifestations if hydroxychloroquine is unsuccessful. ● can be combined with hydroxychloroquine	**Etanercept, Infliximab and Belimumab** ● currently under investigations as treatment options
Short courses of steroid treatment (oral or IM): ● used to treat systemic flare-ups and significant organ manifestations ● can be combined with methotrexate and hydroxychloroquine	**BAFF inhibitors, IF alpha inhibitors and BTK inhibitors** ● currently under investigations as treatment options

Leflunomide, sulfasalazine, azathioprine, and cyclosporine: ● may be given if other treatment options for the rheumatologic manifestations of SS fail	
cyclophosphamide: ● used to treat systemic complications such as cytopenias, lung disease, neuropathy, myelopathy, and vasculitis (if this is unsuccessful then mycophenolate, azathioprine, and methotrexate can be used)	

Another novel treatment approach is the use of human umbilical cord mesenchymal stem cell extracts. They were found to modulate the inflammatory response in rodent models without showing immunogenicity (32).

Chinese medicine treatment

Since these treatment methods of western medicine are often accompanied by severe side effects, some people choose an alternative path according to traditional Chinese medicine. Chinese medicine has been developed over thousands of years and originates in ancient China. Despite the advancement of modern medicine and the constant development of new treatment options and drugs, Chinese medicine is to this day very popular as an alternative approach to the treatment of many diseases. Specialists in Chinese medicine use herbal medicines as well as the traditional Chinese massage tuina, breathing and physical exercises, and acupuncture as a treatment for a multitude of diseases. The main treatment of SS in Chinese medicine is herbal preparations for oral intake, such as the Shengmai powder, Qui Dihuang Pill, or Buzhong Decoction. They are used to treat dryness which is believed to have three main causes. These causes are deficiency of body fluid, obstruction of body fluid, and the reduction in the function of the Zang-Fu organs, which consist of the five Zang organs

liver, heart, spleen, lung, and kidney, as well as the six Fu organs, gallbladder, stomach, small intestine, large intestine, bladder, and sanijao, the triple energizer. These three causes of dryness are thought to be treated by nourishing yin, detoxifying, and removing the blood stasis. In addition to the treatment of dryness, Chinese medicine is also used to treat other aspects of SS, such as fatigue, anxiety and depression, joint pain, as well as lung and kidney manifestations. The practice of Chinese medicine focuses on a holistic approach, intending to improve the patients' overall quality of life. Therefore acupuncture and other external treatments are often used in combination with herbal medicine to increase the therapeutic effect. Research conducted on the effect of Chinese herbal medicine has proven that it does improve the secretory function of salivary glands in humans as well as animals. Other studies have found the positive effect Chinese medicine therapies have on the immune system of SS patients by decreasing BAFF and affecting the cytokine balance (49).

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14. References

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15. Biography

I was born in October 1994 in the south of Germany and grew up near the small town of Ravensburg. Right after graduating high school in 2012, I completed a two-year educational program in retail economics. After finishing the program I went on to travel in Asia and Australia for six months. During this trip, I decided to apply for medicine in Zagreb, and in September of 2015, I started my medical studies at the University of Zagreb, School of Medicine. I am scheduled to graduate in July of 2021.