Chapter 45

Clinical Aspects of Sjögren's

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Introduction and Epidemiology

Sjögren's is an autoimmune inflammatory disorder of the exocrine glands, particularly affecting lacrimal and salivary glands, that can adversely affect quality of life (QOL) and carry a high illness and financial burden.[1,2] Hallmark symptoms are dry mouth and dry eye, often in conjunction with symptoms, such as malaise, profound fatigue, and neurocognitive dysfunction, which patients term "brain fog". However, dry mouth and/or dry eye may not be present at disease initiation, which contributes to the diagnostic challenge and under recognition despite high prevalence of the disease. Various extraglandular manifestations, such as neuropathy, GI dysmotility, arthralgia, and photosensitive skin rashes can be presenting signs of the disease (Table 45-1). The sentinel feature of the disease is lymphocytic infiltration of target organs. In addition to focal lymphocytic infiltration of salivary glands, normal predominately CD4+ T-cells can be found in skin, lung, gastrointestinal (GI) mucosa, and nervous system ganglia.

A recent systematic review estimated the prevalence of Sjögren's in the general population to be 7 per 100 000 person-years,[3] which makes Sjögren's the most common systemic autoimmune disease after rheumatoid arthritis (RA). The disease in likely more prevalent than appreciated with 3.1 million affected persons in the US reported in 2008 by the National Arthritis Data Workgroup.[4] The prevalence doubles when including those with additional connective tissue diseases.[5] The annual incidence, new cases, is 5.8-5.9 per 100,000 as reported from the Mayo

Clinic Olmstead Country Minnesota USA Cohorts.[6] Medical records of primary Sjögren's cases from 1975-2005 and 2006-2015 were examined. The incidence is equivalent to the Taiwan National Health Insurance Bureau claims data, which examined new cases of primary Sjögren's utilizing American European Classification Criteria from 2005-2007, and subsequent review by expert committee resulting in 3352 incident cases.[7] An incidence of 6.0 per 100,000 was observed. Of note in the Taiwan health insurance system, Sjögren's is classified as a "financially catastrophic illness", further underscoring the significant disease burden. Sjögren's is more frequent in women than in men, with a female-to-male ratio of 9:1, but may be under-recognized in men and children. Sjögren's can be the primary condition (primary Sjögren's, or co-occur with another autoimmune disease, such as primary biliary cholangitis, celiac, RA, lupus, or scleroderma (secondary Sjögren's). In primary biliary cholangitis, the prevalence of secondary Sjögren's is approximately 60%, in RA 30%; in lupus 20%. The severity of the Sjögren's manifestations may be similar in both primary and secondary Sjögren's, The Sjögren's component may be minimized when the focus is on another autoimmune disease of perceived greater importance. The overlapping of clinical and serological features, in particular RF and ANA, may also lead to inaccurate diagnosis.[8] Sjögren's is also associated with other organ-specific autoimmune diseases; in particular, autoimmune thyroid disease, which further underscores the autoimmune nature of the disease[9,10,11] Patients with Sjögren's may be restricted in their activities and participation in society, resulting in a reduced health-related QOL[12,13,14,15,1], impaired socioeconomic status,[15] and increased health care costs[16,17,18].

History

The first descriptions of Sjögren's were reported by European clinicians between 1882 and 1925.[19] In 1888, Hadden described a woman with severe dry mouth improving with tincture of

jaborandi, a plant containing pilocarpine.[20] In 1892, Mikulicz observed a man with bilateral parotid and lacrimal gland enlargement that was associated with massive round-cell infiltration. In 1925, Gougerot described three patients with salivary and mucous gland atrophy and insufficiency. In 1933, a Swedish ophthalmologist named Henrik Sjögren reported clinical and histologic findings in 19 women with xerostomia and keratoconjunctivitis sicca (KCS), of whom 13 had chronic arthritis. Seminal work by Morgan, Castleman, Bunim, and Talal in New York and at the National Institutes of Health in the 1950s and 1960s established Sjögren's as an autoantibody-associated autoimmune disorder, detailed its clinical features, and recognized its association with lymphoma.[21]

Clinical Presentation

Glandular Manifestations

Sjögren's affects the exocrine glands, in particular, the lacrimal and salivary glands, resulting in sicca complaints, or dry eyes, and dry oral cavity that can result in dental damage. With respect to the eyes, symptoms of burning, sandy sensations with pain, and photophobia and photosensitivity prevail (Table 45-2). Physical examination reveals chronic irritation and destruction of both corneal and bulbar conjunctival epithelia as a result of disturbed tear quality and production. Accumulation of thick, ropelike secretions along the inner canthus may be the result of decreased tear film and an abnormal mucous component. Untreated, progressive keratitis may result in vision loss. A common problem in patients with dry eye is blepharitis. Conjunctivitis associated with *Staphylococcus aureus* infection may also occur.

Reduced saliva quality and production induces the sensation of dry mouth (xerostomia). It has to be mentioned, however, that a sensation of oral dryness may be present while the salivary secretion is objectively not reduced (although the salivary composition might have been changed),

while patients with objectively being dry may not complain about oral dryness. Typically, such a discrepancy between actual level of salivary secretion and experienced level of oral dryness might be present in about a quarter of the patients. Typical dryness-related complaints in early Sjögren's are predominantly present at rest and during the night. Over time with disease progression, the dryness is also noted during the day.[22] Physical examination shows a decreased salivary pool, "beefy" red tongue with an adherent, sticky mucus coating the erythematous mucosa. The tongue may be smooth with loss of dorsal papillae, or it may have a fissured appearance (Figure 45-1). The lips often appear cracked, peeling, and atrophic and may even appear furrowed or pebbled, and lipstick can adhere to the teeth (central incisors). The buccal mucosa may be pale and corrugated in appearance. Dental caries can occur in atypical locations, especially gum-line (cervical region of the teeth, Figure 45-2), as well as secondary infection of the mucosa with *Candida albicans*. The typical "whitish" appearance of thrush is often lacking, therefore a high index of suspicion is warranted in Sjögren's. Marked inflammation of the corners of the mouth, with skin breakdown, termed angular cheilitis (perleche), can occur. The association is with xerostomia, secondary infections (*Candida albicans*, *Staph aureus*), and iron and vitamin deficiencies (B_2-riboflavin). Enlargement of the salivary glands (parotid, submandibular) may be present and is, generally, due to the presence of an autoimmune inflammatory process. However, enlargement of the glands could be the result of lymphoma development or secondary infection caused by stasis of saliva or salivary duct obstruction.

Dryness also occurs at the mucosal surfaces of the sinuses and upper and lower airways (xerotracheobronchial) resulting in chronic cough and frequent sinus infections. Dryness and pruritis in the vagina leads to dyspareunia, frequent yeast infections, and sexual dysfunction. Major and minor vestibular glands, which secrete the lubricant glairy fluid, can be destroyed.

Dryness in the GI tract leads to atrophic gastritis, constipation and nutritional absorption problems. In particular, the dry skin (xerosis) with its pruritic component affects patient QOL.

Extraglandular Manifestations

Sjögren's is a **systemic** autoimmune disease in which most organs could be affected, giving rise to various extraglandular clinical manifestations[23] (see Table 45-1) (Figures 45-3 and 45-4). The involvement of extraglandular organs can go unrecognized until clinical symptoms become apparent in various stages of the disease, or specialty clinics other than rheumatology may be the primary provider of care. Examples include pulmonary for interstitial lung disease or oncology for lymphoma or multiple myeloma. A Dutch cohort of 140 patients developed a new manifestation or related disease in 30.7% of cases over a 10-year period following diagnosis. Most common manifestations were polyneuropathy, interstitial lung disease, polyarthritis, discoid lupus, and Hashimoto's thyroiditis.[24] In addition, general systemic symptoms such as fatigue, myalgia, and depression are frequently present.

Lymphoma Development

Lymphomas develop in approximately 5-10% of patients with Sjögren's. Moreover, patients with Sjögren's have an 18.8 (CI 9.5 to 37.3) times increased risk of developing lymphomas[25] over the life span. In most cases these are marginal zone B-cell lymphomas occurring in the salivary glands, in particular the parotid gland, the so-called mucosa-associated lymphoid tissue (MALT) lymphoma. These lymphomas are generally localized and follow an indolent, rather benign, clinical course, and if treatment is needed are very responsive to therapy. In a minority of patients, aggressive non-Hodgkin lymphoma (NHL) is present and even Hodgkin disease has been described in Sjögren's. Risk factors for the development of lymphoma include the presence of

systemic activity, cytopenia, cryoglobulins, low complement C4 levels, and palpable purpura.[26] [27] [28] The presence of germinal center–like structures in salivary gland biopsies is highly predictive for the development of lymphoma.[29] Others were not able to confirm these findings for a larger number of mucosa-associated lymphoid tissue (MALT) lymphomas in parotid glands of patients with primary Sjögren's. Isolated salivary gland enlargement, as well as any persistent lymph node swelling (Figure 45-5), and B-cell symptoms in a patient with Sjögren's should raise the suspicion of lymphoma development. There is a 11-fold higher risk of developing hematologic cancers in primary Sjogren's, with B-cell MALT (11%) and myeloid neoplasia/leukemia (6%).[28]

Dermatologic Manifestations

In addition to dry skin (xerosis), many dermatologic conditions can occur in Sjögren's.[30] These include inflammatory, autoimmune, hypersensitivity, fibrosing, vasculitis, and other vascular conditions. Inflammatory conditions include lichen planus, erythema annulare, erythema nodosum (panniculitis), lymphocytic dermatitis, and urticaria. Vitiligo is the autoimmune condition seen in Sjögren's. Hypersensitivity conditions include erythema multiforme with Ig deposition, usually IgM, in superficial microvasculature. The fibrosing condition, lichen sclerosis, can occur on oral or vaginal mucosal surfaces. Small and medium vessel vasculitis, leukocytoclastic vasculitis, urticarial vasculitis, and purpura (flat or palpable). can occur in Sjögren's. Non-inflammatory vascular conditions include Raynaud's, or simply cool fingers and toes, livedo reticularis, petechia, telangectasias, telangectatic matts, and digital infarcts can occur with resultant finger and toe ulcers. Nailfold telangectasias can be observed. Hair loss (alopecia) and hair thinning can be seen. Other skin disorders include localized amyloid, and chilblains (pernio). Decreased perspiration or sweating can occur.

ENT Manifestations

Nasal and throat dryness, and recurrent sinus infections can be a feature of Sjögren's. Thick mucous can be difficult to manage. Hoarseness and even vocal cord polyps (bamboo nodules) can occur. Laryngeal pharyngeal reflux of gastric acid into the upper airway can cause various symptoms and fiberoptic endoscopy can assist the diagnosis. GI reflux disease (GERD) is common in Sjögren's, affecting 60% of patients.[31] Unilateral or asymmetric hearing loss can occur, supporting an immune-mediated etiology. Cranial neuropathy is a feature of Sjögren's, with olfactory (CN I), gustatory (CN IX), auditory/vestibular (CN VIII) nerve involvement, in addition to the most commonly involved trigeminal nerve (CN V).

Parotid gland enlargement can occur in up to 50% of Sjögren's patients, and may be unilateral or bilateral. Ductal stones and mucous plugs can predispose to acute and chronic salivary gland infections. Culturing the secretions can guide treatment and management options, and there can be a role for ductal lavage with or without the aid of sialoendoscopy.[32] Salivary and lacrimal malignancies can occur of several cell types, but most common is MALT lymphoma.

Pulmonary Manifestations

Tracheobronchial dryness can lead to a chronic cough, and increase susceptibility of upper respiratory infections. Chronic thick secretions of mucous can be difficult to clear. A range of lung diseases has been reported in Sjögren's[33]. These include interstitial lung disease (ILD), obstructive lung disease (bronchiectasis, bronchiolitis), cystic lung disease, pleuritis and pleural fibrosis, pulmonary artery hypertension, thromboembolic (pulmonary embolism and anti-phospholipid antibody associated), alveolar hemorrhage, non-tuberculous mycobacterium, and malignancies, especially lymphoma. Imaging studies can show nodules, a reticular interstitial pattern, cysts, pleural effusion or thickening, or small airway disease (bronchiolitis). Incidence of

pulmonary manifestations is 9-20%.[33]. Studies available to evaluate respiratory symptoms in Sjögren's include, pulmonary function testing with diffusion capacity (DLCO), pulse oximetry (rest and exercise), chest x-ray, high resolution chest CT, and echocardiography. Bronchoscopy with biopsy or minimally invasive chest surgery (VATS) may occasionally be needed to further assist in diagnosis. Although rare, amyloid lesions, both endobronchial and parenchymal are seen[34]. Sjögren's patients experience recurrent pulmonary infections, bronchitis and pneumonia (10-35%), and underlying primary immune deficiency may be a co-factor. ILD carries the greatest risk for morbidity and mortality[35]. Nonspecific interstitial pneumonitis (NSIP) with a fibrosing phenotype occurs in 45% of cases, with both lymphocytic interstitial pneumonitis (LIP) and usual interstitial pneumonitis (UIP) occurring in approximately 15% of ILD cases. Smoking should be avoided. Other causes of dyspnea and sleep apnea should be considered.

Peri-operative management is extremely important in patients undergoing most procedures to avoid complications (corneal abrasions) and facilitate patient comfort, especially with regard to dry eye and dry mouth and throat. The patient's preference of lubricants and focus on humidification are most important. Minimizing drying medications, oscillatory positive expiratory pressure, nebulized-bronchodilators, hypertonic saline, or acetylcysteine (mucolytic) are options, as is co-management between Sjögren's expert, surgeon, and anesthesiologist.

Joint and Muscle Manifestations

The spectrum of musculoskeletal manifestations in Sjögren's range from mild arthralgia and myalgia to synovitis with chronic pain. Although common, the polyarticular inflammatory arthritis (50%) in Sjögren's is rarely debilitating or erosive. Rarely, myositis can occur.

Gastrointestinal Manifestations

GI symptoms are common in primary Sjögren's patients, with up to 90% of patients reporting a GI related symptom[36]. GI motility abnormalities underlie many of the symptoms ranging from dysphagia to constipation, and exocrine dysfunction in the GI system includes, pancreatic dysfunction with 18-37.5% having some degree of exocrine insufficiency[37], although steatorrhea is uncommon. Severe dysphagia occurs in 40% of patients with contributions from decreased saliva, esophageal webs, low-grade myositis, and esophageal dysmotility[38]. The increased incidence of GERD is well recognized, occurring in 60% of patients vs 23% in controls[31]. Dysregulation of innervation of the lower esophageal sphincter (LES) leads to increased LES pressure. Gastroparesis occurs in 29-70% of patients with 16% exhibiting an autonomic neuropathy, and may correlate with IgG levels and sedimentation rate. *Helicobacter pylori* should be excluded and treated to prevent chronic antigenic stimulus leading to MALT lymphoma. Irritable bowel symptoms occur in 39% of patients, and celiac disease may co-occur with Sjögren's, but a gluten free diet does not improve sicca symptoms. Antibodies to gonadotropic releasing hormone (GnRH) have been found, affecting the myenteric plexa of the GI wall[38]. The liver may be a target organ with autoimmune hepatitis occurring in 0-1.7% of patients. Abnormal liver function tests are common (49%), but mild[36]. Primary biliary cholangitis (PBC) occurs in 2-7% of Sjögren's patients, with SSA/SSB antibodies rarely found. Sicca symptoms and salivary gland histopathology, and sialometry or sialogram abnormalities in PBC are common, 58-93% and 22-64%, respectively[36]. Sjögren's carriers a high burden of GI manifestations, however this association remains under appreciated in clinical practice.

Gynecologic and Urologic Manifestations and Pregnancy

Women with primary Sjögren's have impaired sexual function and more sexual distress compared with healthy controls. Vaginal and vulvar dryness lead to dyspareunia and yeast infections. Major and minor vestibular gland blockage and lymphocytic infiltration, CD4+ T-cell predominate, with gland destruction can occur. Human papilloma virus can lead to cervical dysplasia or cancer in the setting of immune dysregulation. Thus, monitoring is necessary even in older and non-sexually active patients. Interstitial cystitis (IC) occurs in 9% of Sjögren's, having a major impact on QOL for some. SSA antibody directed toward the M3 receptor in bladder musculature has been reported. Additional pelvic pain conditions result from neurologic involvement (pudendal neuropathy), or endometriosis (4-fold increase). Primary ovarian failure may occur in up to 20% of young Sjögren's cases resulting in infertility, and ovarian antibodies have been detected.

If SSA antibody is detected, pregnancy is co-managed with high-risk obstetrics for optimal outcome. Autoantibodies cross the placenta at 12 weeks gestation. Potential effects include myocarditis with fibrosis and blockage of apoptosis of remodeling cardiac cells, which can lead to arrhythmia and congenital heart block (CHB). The CHB may require a fetal pacemaker, however potential risk is low (2%), unless CHB occurred in a prior pregnancy, then the risk increases to 20%.[39] [40] Presence of anti-phospholipid antibodies may warrant low-dose aspirin during pregnancy.

Kidney Manifestations

Interstitial nephritis is observed in 30% of patients and leads to clinical symptoms in 5% to 10% of patients. Distal or proximal renal tubular acidosis (RTA) type I or II can result in clinical symptoms such as compromised renal function, proteinuria, nephrocalcinosis, renal stones, hypokalemia, hypophosphatemia, polyuria, and nephrogenic diabetes insipidus. An immune complex–mediated mesangial proliferative or membranoproliferative nephritis is seen in 5% to

10% of the patients, leading to clinical findings such as hypertension, proteinuria (mild to nephritic syndrome), and active urine sediment with erythrocytes and casts.

Neurologic Manifestations

Central nervous system manifestations can occur, but full characterization is still needed. Original cases series from the 1980's remain controversial[41]. Peripheral nervous system involvement affects approximately 10% to 20% of patients with Sjögren's, mainly in the form of sensory and sensorimotor polyneuropathies and cranial neuropathies.[42] [43] Stabilization or spontaneous improvements are seen. Small fiber neuropathy may be the most common neuropathic process seen in Sjögren's, and has a diverse presentation[44]. Skin biopsy with nerve and sweat fiber staining may aid in establishing the diagnosis of Sjögren's, especially in the absence of SSA/SSB antibodies. Single or multiple mononeuropathies can occasionally occur, and nerve biopsies can reveal vasculitis.[45]

New technologies, such as high-resolution magnetic resonance neurography, may prove useful in diagnosing ganglionopathies seen in Sjögren's[46]. Mild autonomic neuropathy is not uncommon in Sjögren's and can impact exocrine secretion, orthostasis, GI, and bladder function.[47]

Vasculitis

Skin lesions based on vasculitis are observed in 10% of patients with primary Sjögren's. Purpura, polymorphic erythema, urticarial lesions, and ulcers caused by leukocytoclastic vasculitis are seen most often. Medium vessel vasculitis occurs less commonly (5%).[48] Systemic vasculitis can lead to neuropathic, renal, pulmonary, and gastrointestinal symptoms. These manifestations are often associated with cryoglobulinemia and low complement levels.[49]

Cardiovascular

Systemic inflammatory autoimmune diseases are associated with increase risk of cardiovascular disease. An increase in cerebrovascular and myocardial infarct events occur in primary Sjögren's.[7 50]

Hematologic Manifestations

Common hematologic complications are mild autoimmune cytopenias and hyperglobulinemia. No specific therapy is necessary, although these patients require careful follow-up. For more severe cytopenias, autoimmune hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, and agranulocytosis treatment may be necessary. Leukopenia occurs in 20% of cases, and can serve as a clue to the diagnosis of Sjögren's. Infections do not occur more frequently in this group.

Men with Sjögren's

Men constitute at least 10% of Sjögren's. Thus, a substantial number of men have the disease. Overall prevalence ranges from 3-4 million, when secondary Sjögren's is included this increases to at least 6 million. Thus, up to 600,000 men may suffer in the US alone. Men are underdiagnosed due to low suspicion and lower incidence of the classic autoantibodies, SSA and SSB. Further evidence that the prevalence and incidence is higher than currently appreciated is found in Taiwan national insurance data base report of overall incidence of 6.0 per 100,000 with 1.1 per 100,000 for males,[7 51] and a Hungarian report of female to male ratio of 7:1 in a series of 60 cases identified by EACC.[51] In the Taiwan group, mortality was 3-fold greater in men compared to women, and was related to cardiovascular disease.[7] The Hungarian group noted increase disease severity and higher incidence of arthritis, vasculitis, and lymphadenopathy in men.[51] An increase in vasculitis and interstitial nephritis, in addition to serious ocular complications compared to women, was found in a separate cohort. Further, men were more likely to be negative for SSA, SSB, and ANA antibodies than women (36% vs 11%)[52]. It is not

yet clear if Sjögren's in men and children presents and evolves the same as in women. Published reports of the disease in men note dry eye, dry mouth, dry skin, joint pain, and fatigue, in addition to a wide-range of EGM. Urethritis and prostatitis can be present, as well as symptoms suggesting IC, including suprapubic pain, urgency, frequency, and nocturia.

Three of four small published case series, found lower incidence of SSA/B antibodies.[53] [54] [55] SSB antibody positive patients have been reported not to meet the classic ACR-EULAR CC phenotype,[56] and the final version of this classification criteria does not include SSB, or ANA plus RF positivity.[57] However, in the clinical setting SSB alone is observed in males with a focus score ≥ 1.0 (Table 45-3). Larger well characterized data sets of male patients will be needed to understand the spectrum of the disease in men. Data utilizing novel autoantibodies included in the Sjo™ diagnostic test may assist in diagnosis in early disease, especially in SSA/B negative cases.[58] These novel antibodies target antigens found in salivary glands, which include salivary protein-1, carbonic anhydrase-6, and parotid specific protein.

Childhood Sjögren's

Sjögren's in childhood is likely more common than has been appreciated. Greater than 200 cases appear in the literature[59]. Sicca symptoms were less common (36.9%) than in adults (85-90%), and parotitis common (59.5%). Parotid gland enlargement may be the most specific clinical marker of Sjögren's in children, and trigger testing for SSA/B antibodies. Other features included arthritis or arthralgia (36%), neuropsychiatric manifestations (10%), RTA (7%), interstitial nephritis (6%), renal failure (2%). Additional manifestations included neuromyelitis optica, rash, myositis, serositis, Raynaud's, lymphadenopathy, fever, and fatigue. Children specific diagnostic and research classification criteria are needed.[60] Current findings suggest the SSA and/or SSB

antibodies are common (95%), and focal lymphocytic sialadenitis is often present, but may have a FS < 1.0.[61]

Serologic Findings

The most characteristic autoantibodies in Sjögren's are anti–Sjögren syndrome antigen A (anti-SSA/Ro) antibodies, present in 70% of patients, and anti–Sjögren syndrome antigen B (anti-SSB/La) antibodies, present in approximately 50% of patients. High titers of these autoantibodies, in particular anti-SSB/La antibodies, are associated with extraglandular disease. Anti-SSB/La antibodies are considered to be the most specific serologic marker for Sjögren's, although they can also be found in 25% to 35% of patients with SLE or other autoimmune connective-tissue disorders and in approximately 5% of healthy individuals. Anti–alpha-fodrin autoantibodies occur in approximately 30% of patients with Sjögren's and are considered specific for the disease. Autoantibodies to human muscarinic acetylcholine receptor 3 are present in 90% of patients with primary Sjögren's and 71% of patients with secondary Sjögren's; however, they are not specific for Sjögren's, because they are also present in 65% and 68% of patients with RA and SLE, respectively.[62] The rheumatoid factor is present in approximately 50% of patients but has a very low specificity for Sjögren's. Between 10% and 20% of patients with Sjögren's demonstrate mixed essential cryoglobulins. The presence of cryoglobulins is associated with vasculitic manifestations such as purpura, polyneuropathy/mononeuritis multiplex, and glomerulonephritis, and they constitute a risk factor for the development of lymphoma. Hypergammaglobulinemia, present in 40% of patients, reflects polyclonal B-lymphocyte activation, which is characteristic of Sjögren's.[63] In addition, monoclonal gammopathy, reported in 22% of patients, demonstrates excessive clonal B-cell proliferation and is associated with the development of lymphoma.

Ultrasound of Glands

Ultrasound of major salivary glands (sUS) is an upcoming diagnostic method when it comes to assessing involvement of major salivary glands in Sjögren's syndrome, both with regard of diagnostics, disease monitoring and assessing disease activity. sUS is well tolerated, non-invasive, inexpensive, non-irradiating and widely available in the rheumatologic outpatient clinics, but its reliability depends greatly on its operator. A recent meta-analysis assessing the diagnostic properties of sUS in pSS reported a pooled sensitivity of 69% and specificity of 92%. This meta-analysis also revealed a large clinical and methodological heterogeneity between studies, which not only hampered interpretation of pooled outcomes but also influenced the results reported in the various studies. Thus, the possible role of sUS in the diagnosis of pSS is promising, but remains unclear and needs further study.

Classification and Diagnosis of Sjögren's

Many classification criteria for Sjögren's have been utilized over the years. The 2002 revised American European Consensus Group (AECG) research classification criteria for Sjögren's are still widely used (Box 45-1). These criteria combine subjective symptoms of dry eyes and dry mouth with the objective signs of KCS and xerostomia.[64] In 2012, a new set of criteria focused on objective measures was provisionally endorsed by the American College of Rheumatology (ACR). Subsequently, an International Sjögren's Syndrome Criteria Working Group, facilitated by the Sjögren's Syndrome Foundation www.sjogrens.org, developed validated consensus criteria that were published in 2016 and were endorsed both by European League Against Rheumatism (EULAR) and ACR[57]. These two research classification systems exhibit a high degree of concordance, sensitivity, and specificity when compared to each other and to expert clinician opinion (Box 45-1). These new criteria are a step in the right direction, but further refinement would increase their utility.

The subjective ocular and oral symptoms, classification criteria in the AECG criteria that have evolved to an entry criterion in the ACR-EULAR classification criteria, are obtained by history taking. Two tests are used to objectify reduced tear production. In the Schirmer test a piece of filter paper is placed laterally on the lower eyelid, which results in wetting due to tear production. If less than 5 mm of the paper is wetted after 5 minutes, then the test result is considered positive (Figure 45-6). In the rose bengal test, dye stains devitalized areas of the cornea and conjunctiva, which can then be scored using a split lamp. A rose bengal score of ≥4 according to the van Bijsterveld scoring system is considered abnormal. Instead of rose bengal stain, lissamine green can be used, which shows comparable results and is less painful. The ocular staining score (OSS) uses fluorescein (staining of cornea) in addition to lissamine green staining (staining of conjunctiva). An additional test, which is not accepted as a diagnostic technique for Sjögren's but provides a global assessment of the function of the tear film, is the tear break-up time test. This test is performed by measuring break-up time after the instillation of fluorescein. An interval of less than 10 seconds is considered abnormal.

Currently, the most commonly applied noninvasive objective salivary gland diagnostic test is measuring the flow rate of unstimulated whole saliva, it is included in the AECG and ACR-EULAR classification criteria. The patient is asked to expectorate once and then collect all saliva into a graduated container during a 15-minute period. Results obtained by sialometry, regardless of the presence of oral complaints, allow monitoring of the disease progression.[22] If more specific functional information is required for a particular gland, for research purposes and for patient-based advice on how best to reduce xerostomia, then individual gland collection techniques can be used (Figures 45-7 and 45-8). Salivary gland ultrasonography is not yet included in either the

AECG and ACR-EULAR classification criteria. Further study is needed to add sUS to the classification criteria.

To confirm the diagnosis of Sjögren's histopathologically, usually a biopsy from a labial salivary gland is taken. The diagnosis can be confirmed if this biopsy shows focal lymphocytic sialadenitis with a focus score, defined as an accumulation of 50 or more lymphocytes per 4 mm^2, of ≥1.[65] Recently, it has been shown that parotid biopsies might serve as a proper alternative in the diagnosis of Sjögren's. In such biopsies, MALT or NHL pathologic findings are easier to detect because parotid glands are more commonly affected,[66] and the same gland can be biopsied more often.[67] Imaging studies can also be used to evaluate salivary gland involvement. Sialography of the parotid gland has a high diagnostic accuracy. The main characteristic of Sjögren's is a diffuse collection of contrast fluid at the terminal acini of the ductal tree, called *sialectasia*.[68] [69] With scintigraphy, patients with Sjögren's demonstrate decreased uptake and release of technetium (Tc)–99m pertechnetate.[70] Both sialography and salivary scintigraphy are not anymore included in the ACR-EULAR classification criteria. Finally, as mentioned before, sUS is a promising, less-invasive alternative to sialography in the classification of Sjögren's.[71]

The presence of nonspecific serologic markers of autoimmunity such as antinuclear antibodies, rheumatoid factors, and elevated immunoglobulins (particularly IgG) are important contributors to a definitive diagnosis of Sjögren's.[72] In the ACR-EULAR classification criteria only positivity for anti-Ro/SSA is used as a criterion.

Hormonal Factors

Sjögren's is more common among women than men. X-chromosome silencing and sex steroids probably play important roles in the pathogenesis of Sjögren's.[73] Many genes on the X

chromosome are involved in the immune system, and impaired inactivation of the genes on the X chromosome may contribute to the development of autoimmune disease. Sex hormones have key roles in the function of cells of the immune system. Estrogens appear to have positive effects on the emergence of autoimmune disease, and androgens have a more protective role, although the mechanisms still are not well understood. Patients with Sjögren's appear to be androgen deficient and have lower serum concentrations of dehydroepiandrosterone (5-DHEA) and its sulfate ester, dehydroepiandrosterone-sulfate (DHEA-S).[74] [75] [76] Sex hormones also influence saliva and tear production.

Sjögren's in Patients with Lupus

The association of Sjögren's and SLE was first noted in 1959. Small-scale studies suggested the prevalence of Sjögren's in SLE ranging from 7% to 35%. Several large-scale studies have analyzed the influence of Sjögren's on SLE. In one study, 9.2% of 283 patients with SLE who were Greek met the AECG classification criteria for Sjögren's.[77] Patients with SLE who had Sjögren's tended to be older, have a higher prevalence of Raynaud phenomenon, rheumatoid factor, anti-SSA and anti-SSB, and a high frequency for the DRB1*0301 allele. These patients had less renal disease, adenopathy, and thrombocytopenia. Of the patients with SLE who were Norwegian, 81 patients over the age of 70 years were compared with matched individuals with RA and healthy control participants.[78] The SLE group had more fatigue, anti-SSA and anti-SSB antibodies, and a positive Schirmer test. In the Johns Hopkins study, 259 (14%) of the 1531 patients with SLE were found to have Sjögren's by clinical evaluation.[79] These patients were generally older, white women with more photosensitivity; oral ulcers; Raynaud phenomenon; less renal disease; and anti-SSA and anti-SSB, anti–double-stranded DNA (anti-dsDNA), and anti-ribonucleoprotein (anti-RNP) antibodies. Approximately 20% of more than 2000 patients with

lupus who were of Chinese descent at Peking Union Medical College also had Sjögren's.[78] Significant differences between those with Sjögren's/SLE and those with SLE only included older age, female gender, and higher rates of sicca symptoms and signs, renal tubular acidosis, and interstitial lung disease in the former. Patients with SLE only had more rash, nephrosis, central nervous system disease, lower IgG levels, more disease activity, and more immune suppressive and corticosteroid use. Seventy-one percent of the patients with Sjögren's/SLE were SSA or SSB positive versus 20% of those with SLE. In summary, patients with Sjögren's/SLE who met Sjögren's criteria made up approximately 10% of the SLE population, although twice that many have features of Sjögren's. These patients tend to be older and, Caucasian, to have a more benign process, and to less frequently require aggressive management. For further details regarding Sjögren's in patients with lupus also see chapter 32.

Outcome Measures

After years of inactivity, numerous clinical trials for Sjögren's are underway. The best validated methods of ascertainment and outcome measures are the following[80 81 82 83 84 85 1]:

1. Salivary gland function (salivary flow rate) and biomarkers (cathepsin D, alpha-enolase, and beta-2 microglobulin)
2. Lacrimal gland function (Schirmer test, lissamine green test, and tear breakup time)
3. Laboratory assessments (quantitative immunoglobulins and rheumatoid factor)
4. Subjective assessments (fatigue inventories and short form–36 [SF-36])
    a. Patient Numeric Rating Scale (NRS) scores for eye, mouth, vaginal dryness
    b. Subject global assessment of disease activity (subGDA)
    c. Physician global assessment of disease activity (phyGDA)
5. Extraglandular manifestations (scored by organ system)

6. Composite scores (Sjögren Syndrome Disease Activity and Damage Index, the EULAR Sjögren Syndrome Disease Activity Index [ESSDAI], and the EULAR Sjögren Syndrome Patient Reported Index [ESSPRI]) and Sjögren's Syndrome Responder Index (SSRI)
7. Work Productivity and Activity Impairment (WPAI-GH)
8. Vaginal Dryness Numeric Rating Scale (Vaginal NRS)
9. Female Sexual Function Index (FSFI)
10. PROMIS Fatigue Short Form

Prognosis

Early, accurate diagnosis of Sjögren's (Figure 45-9) can help prevent or ensure adequate treatment of many of the complications associated with the disease and may contribute to prompt recognition and treatment of serious systemic complications of Sjögren's.[22,23] The early diagnosis and management of Sjögren's is expected to improve outcome. Also, the prognosis depends on the target organ involved and disease severity. Management of patients with Sjögren's should ideally involve a multidisciplinary team that consists of a specialized rheumatologist, oral and maxillofacial surgeon, and/or dentist, ophthalmologist, pathologist, pulmonologist, gastroenterologist, neurologist, hematologist, oral hygienist and nutritionist. With a proactive and multi-disciplinary treatment plan, the QOL of Sjögren's patients can be significantly improved and burden of illness reduced.

FIGURE 45-1 Reduced saliva quality and quantity induces dry mouth (xerostomia), which may lead to the development of an arid, furrowed tongue.

FIGURE 45-2 Hyposalivation-related dental caries. Note the carious destruction of the cervical regions of the teeth, areas that are relatively resistant to caries in patients with normal salivary secretion, because the self-clearance of the oral cavity is reduced.

FIGURE 45-3 Purpura as an extraglandular manifestation.

FIGURE 45-4 Raynaud phenomenon occurring in a patient with Sjögren's.

FIGURE 45-5 Swollen parotid gland from the development of mucosa-associated lymphoid tissue (MALT) lymphoma.

FIGURE 45-6 Schirmer test. A piece of filter paper is placed inside the lower eyelid (conjunctival sac). The eyes are closed for 5 minutes. The paper is then removed, and the amount of moisture is measured. In contrast to what is illustrated in this figure, usually the strips are placed laterally and the patient is asked to look upward so that no corneal abrasion occurs (when the eyes close, the eyeball rotates upward).

FIGURE 45-7 Collection of glandular saliva. **A,** A Lashley cup is used to collect parotid saliva. The cup contains a central chamber for collecting the saliva and a peripheral chamber to which a slight underpressure can be applied to keep the cup in place over the orifice of the parotid gland. **B,** The Lashley cup is in place on the orifice of the parotid gland. The secretion of parotid saliva is noted in one of the tubes connected to the cup. The other tube is used for applying slight underpressure. **C,** By blocking both orifices of the parotid gland, saliva collecting on the floor of the mouth can be removed by a syringe to assess submandibular/sublingual flow while collecting parotid saliva.

FIGURE 45-8 Relation among disease duration (i.e., the time from first complaints induced by or related to oral dryness until referral), mean salivary flow rates (mean ± SEM), unstimulated whole saliva (UWS), and submandibular/sublingual glands (SM/SL).[16]

FIGURE 45-9 Diagnostic workup strategy for patients referred to the University Medical Center Groningen, The Netherlands, under clinical suspicion of Sjögren's. The primary referral is done by dentists, general practitioners, or other specialists. Before the first visit, patients receive written information about the diagnostic procedure followed at our institution.

Table 45-1 Estimated Prevalence of a Particular Extraglandular Manifestation among Patients with Sjögren's[23,86,87,88]

AFFECTED ORGAN SYSTEM	EXTRAGLANDULAR MANIFESTATIONS	ESTIMATED PREVALENCE (%)*
Joints and muscles	Arthralgia or arthritis	>50
	Myopathy	□□
Skin	Xerosis	>50
	Purpura	10
	Other skin lesion (e.g., erythema nodosum, livedo reticularis, lichen planus, vitiligo, cutaneous amyloidosis, and granuloma annulare)	<5
	Raynaud phenomenon	13-30
Cardiovascular	Pericarditis	Up to 30
Respiratory tract	Interstitial lung disease (generally mild)	30

AFFECTED ORGAN SYSTEM	EXTRAGLANDULAR MANIFESTATIONS	ESTIMATED PREVALENCE (%)*
	Mucosa-associated lymphoid tissue (MALT) lymphoma	□□
Gastrointestinal tract	Dysphagia	>50
	Esophageal involvement	□□
	Gastritis	20
Nervous system	Peripheral neuropathy | Small fiber neuropathy	≥20
	Cranial neuropathy	5
	Central nervous system (CNS) involvement (focal or generalized)	Up to 20
Urogenital tract	Interstitial nephritis | Renal tubular acidosis	25
	Glomerulonephritis (associated with cryoglobulinemia)	<10
	Interstitial cystitis	4

*Percentages greatly differ among studies.

Table 45-2 Onset and Duration of Symptoms of Eye and Mouth Dryness in Patients with and without Sjögren's[89]

	Primary Sjögren's	Secondary Sjögren's	Sjögren's	Non-Sjögren's
	(n = 32)	**(n = 25)**	**(n = 57)**	**(n = 23)**
Onset of first complaints, number (%)				
Eye dryness before mouth dryness	5 (16)	10 (40)	15 (26)	3 (13)
Eye dryness only	1 (3)	2 (8)	3 (5)	2 (9)
Mouth dryness before eye dryness	10 (31)	5 (20)	15 (26)	3 (13)
Mouth dryness only	2 (6)	2 (8)	4 (7)	3 (13)
Simultaneous onset	11 (34)	6 (24)	17 (30)	9 (39)
Neither eye nor mouth dryness	3 (10)	0	3 (5)	3 (13)
Duration at first visit, median, months				
Eye dryness	38	50	43	31
Mouth dryness	44	34	39	31

Box 45-1 2002 Revised American European Consensus Group (AECG) Research Classification Criteria and the 2016 ACR/EULAR Classification Criteria for Primary Sjögren's

AECG Classification Criteria (2002)	ACR/EULAR Classification Criteria (2016)
Classification as Primary Sjögren's*	

Any 4 of 6 items as long as either IV or VI is (+) OR Any 3 of the 4 objective criteria (III, IV, V, VI)	Classification as Primary Sjögren's* Score of ≥ 4 when the weights of the 5 items are added

I. Subjective Dry Eyes (≥1):	**Entry Criteria:**	**Scor**
Have you had daily, persistent, troublesome dry eyes for more than 3 months?	At least one symptom of dry eye OR dry mouth based on a positive response to one of the 5 AECG standardized questions (removed question: Have you had recurrently or persistently swollen salivary glands as an adult?)	
Do you have a recurrent sensation of sand or gravel in the eyes?		
Do you use tear substitutes more than 3 times a day?		
II. Subjective Dry Mouth (≥1):	OR	
Have you had a daily feeling of dry mouth for more than 3 months?	Suspicion of Sjögren's based on activity on at least one domain of the ESSDAI	
Do you frequently drink liquids to aid in swallowing dry food?	**Weighted Items:**	
Have you had recurrently or persistently swollen salivary glands as an adult?	**I. Histopathology:**	**3**
III. Ocular signs (≥1):	Focus Score ≥1	
vBS ≥ 4	**II. Autoantibodies:**	**3**
Schirmer's I test ≤ 5 mm/5 min	Anti-Ro/SSA (+)	
IV. Histopathology:	**III. Ocular Staining (≥1):**	**1**
Focus Score ≥1	vBS ≥ 4	
V. Salivary gland involvement:	OSS ≥ 5	

WUSF ≤ 1.5 ml/15 min	**IV. Lacrimal Dysfunction:**	**1**
VI. Autoantibodies (≥1):	Schirmer's I test ≤ 5 mm/5 min	
Anti-Ro/SSA (+)	**V. Salivary gland involvement:**	**1**
Anti-La/SSB (+)	WUSF ≤ 1.5 ml/15 min	

* In absence of other associated diseases or exclusion criteria. For AECG: 1) prior head and neck radiation treatment, 2) hepatitis C infection, 3) acquired immunodeficiency disease, 4) preexisting lymphoma, 5) sarcoidosis, 6) graft-versus-host disease, 7) immediate prior anticholinergic drug use. For ACR/EULAR: includes items 1, 2 (confirmation by PCR), 3, 5, and 6. Amyloidosis and IgG4-related disease are exclusions. Prior lymphoma or use of anticholinergic drugs are not exclusions.[64 57]

vBS: van Bijsterveld score; OSS: ocular staining score; WUSF: whole unstimulated saliva flow

REFERENCES

[1] Cornec D, Devauchelle-Pensec V, Mariette X et al. Severe health-related quality of life impairment in active primary Sjögren's syndrome and patient-reported outcomes: data from a large therapeutic trial. *Arthritis Care Res* 69(4):528-535, 2017.

[2] Sjögren's Syndrome Foundation. Living with Sjögren's: summary of major findings. *Sjögren's Quarterly* 12(2):1,6-9, 2017.

[3] Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clin Epidemiol* 30(6):247-255, 2014.

[4] Helmick CG, Felson DT, Lawrence RC et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part 1. *Arthritis Rheum* 58(1):15-25, 2008.

[5] Fox RI, Stern M, Michelson P. Update in Sjögren syndrome. *Curr Opin Rheumatol* 12(5):391-398, 2000.

[6] Maciel G, Crowson CS, Matteson EL et al. Incidence and mortality of physician-diagnosed primary Sjögren syndrome: time trends over a 40-year period in a population-based US Cohort. *Mayo Clin Proc* 92(5):734-743, 2017.

[7] Weng MY, Huang YT, Liu MF et al. Incidence and mortality of treated primary Sjogren's syndrome in Taiwan: a population-based study. *J Rheumatol* 38(4):706-708, 2011.

[8] Rasmussen A, Radfar L, Lewis D et al. Previous diagnosis of Sjögren's syndrome as rheumatoid arthritis or systemic lupus erythematosus. *Rheumatology (Oxford)* 55(7):1195-1201, 2016.

[9] Fox RI. Sjogren's syndrome. *Lancet* 366(9482):321-331, 2005.

[10] Hansen A, Lipsky PE, Dorner T: Immunopathogenesis of primary Sjogren's syndrome: implications for disease management and therapy. *Curr Opin Rheumatol* 17(5):558–565, 2005.

[11] Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. *Semin Arthritis Rheum* 36(4):246-255, 2007.

[12] Strömbeck B, Ekdahl C, Manthorpe R et al. Health-related quality of life in primary Sjögren's

syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. *Scand J Rheumatol* 29:20-28, 2000.

[13] Valtýsdóttir ST, Gudbjörnsson B, Lindqvist U et al. Anxiety and depression in patients with primary Sjögren's syndrome. *J Rheumatol* 27:165-169, 2000.

[14] Segal B, Bowman SJ, Fox PC et al. Primary Sjögren's syndrome:health experiences and predictors of health quality among patients in the United States. *Health Qual Life Outcomes* 7:46, 2009.

[15] Meijer JM, Meiners PM, Huddleston Slater JJ, et al: Health-related quality of life, employment and disability in patients with Sjogren's syndrome. *Rheumatology (Oxford)* 48(9):1077–1082, 2009.

[16] Bowman SJ, St Pierre Y, Sutcliffe N et al. Estimating indirect costs in primary Sjögren's syndrome. *J Rheumatol* 37:1010-1015, 2010.

[17] Callaghan R, Prabu A, Allan RB et al. Direct health-care costs and predictors of costs in patients with primary Sjögren's syndrome. *Rheumatology (Oxford)* 46:105-111, 2007.

[18] Fox PC, Bowman SJ, Segal B et al. Oral involvement in primary Sjögren's syndrome. *J Am Dent Assoc* 139:1592-1601, 2008.

[19] Talal N: Sjögren's syndrome: an historical perspective. *Ann Med Interne (Paris)* 149(1):4–6, 1998.

[20] Hadden WB. On dry mouth, or suppression of the salivary and buccal secretion. *Transaction of the Clinical Society of London.* Longmans Green & Co, London England. 5:176-179, 1888.

[21] Bloch KJ, Buchanan WW, Wohl MJ, et al: Sjoegren's syndrome. A clinical, pathological, and serological study of sixty-two cases. *Medicine (Baltimore)* 44:187–231, 1965.

[22] Pijpe J, Kalk WW, Bootsma H, et al: Progression of salivary gland dysfunction in patients with Sjogren's syndrome. *Ann Rheum Dis* 66(1):107–112, 2007.

[23] Kassan SS, Moutsopoulos HM: Clinical manifestations and early diagnosis of Sjogren syndrome. *Arch Intern Med* 164(12):1275–1284, 2004.

[24] Ter Borg EJ, Kelder JC. Development of new extra-glandular manifestations or associated auto-immune diseases after establishing the diagnosis of primary Sjögren's syndrome: a long-term study of the Antonius Nieuwegein Sjögren (ANS) cohort. *Rheumatol Int* April 19, 2017. doi:10.1007/s00296-017-3715-4. [Epub ahead of print]

[25] Zintzaras E, Voulgarelis M, Moutsopoulos HM: The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 165(20):2337–2344, 2005.

[26] Theander E, Henriksson G, Ljungberg O, et al: Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 65(6):796–803, 2006.

[27] Voulgarelis M, Skopouli FN: Clinical, immunologic, and molecular factors predicting lymphoma development in Sjogren's syndrome patients. *Clin Rev Allergy Immunol* 32(3):265–274, 2007.

[28] Brito-Zerón P, Kostov B, Fraile G et al. SS Study Group GEAS-SEMI. Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. *J Hematol Oncol* 10(1):90, 2017.

[29] Theander E, Vasaitis L, Baecklund E, et al: Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjogren's syndrome. *Ann Rheum Dis* 70(8):1363–1368, 2011.

[30] Soy M, Piskin S. Cutaneous findings in patients with primary Sjögren's syndrome. *Clin Rheumatol* 26:1350-1352, 2007.

[31] Mandl T, Ekberg O, Wollmer P et al. Dysphagia and dysmotility of the pharynx and

oesophagus in patie nts with primary Sjögren's syndrome. *Scand J Rheumatol* 36:394-401, 2007.

[32] DeLuca R, Trodella M, Vicidomini A et al. Endoscopic management of salivary gland obstructive diseases in patients with Sjögren's syndrome. *J Craniomaxillofac Surg* 43(8):1643-1649, 2015.

[33] Flament T, Bigot A, Chaigne B et al. Pulmonary manifestations of Sjögren's syndrome. *Eur Respir Rev* 25(140):110-123, 2016.

[34] Rajagopala S, Singh N, Gupta K et al. Pulmonary amyloidosis in Sjögren's syndrome: a case report and systematic review of the literature. *Respirology* 15(5):860-866, 2010.

[35] Nannini C, Jebakumar AJ, Crowson CS et al. Primary Sjogren's syndrome 1976-2005 and associated interstitial lung disease: a population-based study of incidence and mortality. *BMJ Open* 3(11):e003569, 2013.

[36] Ebert EC. Gastrointestinal and hepatic manifestations of Sjogren syndrome. *J Clin Gastroenterol* 46(1):25-30, 2012.

[37] Afzelius P, Fallentin EM, Larsen S et al. Pancreatic function and morphology in Sjögren's syndrome. *Scand J Gastroenterol* 45(6):752-758, 2010.

[38] Ohlsson B, Scheja A, Janciauskiene S et al. Functional bowel symptoms and GnRH antibodies: common findings in patients with primary Sjögren's syndrome but not in systemic sclerosis. *Scand J Rheumatol* 38(5):391-393, 2009.

[39] Julkunen H, Eronen M. The rate of isolated congenital heartblock: a population-based study. *Arthritis Rheum* 44:487-488, 2001.

[40] Brucato A, Cimaz R, Caporali R et al. Pregnancy outcomes in patient's with autoimmune diseases and anti-Ro/SSA antibodies. *Clin Rev Allergy Immunol* 40(1):27-41, 2011.

[41] Alexander EL, Provost TT, Stevens MB et al. Neurologic complications of primary Sjögren's syndrome. *Medicine (Baltimore)* 61(4):247-257.

[42] Font J, Ramos-Casals M, de la Red G et al. Pure sensory neuropathy in primary Sjögren's

syndrome. Longterm prospective followup and review of the literature. *J Rheumatol* 30(7):1552-1557, 2003.

[43] Birnbaum J. Peripheral nervous system manifestations of Sjögren's syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. *Neurologist* 16(5):287-297, 2010.

[44] Carteron N, Wright MD, Mandel S. Small fiber neuropathy and Sjögren's: a view from the rheumatologist, a view from the neurologist. *Sjögren's Quarterly* 9(3):1,2,4,5.

[45] Gorson KC, Natarajan N, Ropper AH, et al: Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial. *Muscle Nerve* 35(1):66–69, 2007.

[46] Birnbaum J, Duncan T, Owoyemi K et al. Use of a novel high-resolution magnetic resonance neurography protocol to detect abnormal dorsal root Ganglia in Sjögren patients with neuropathic pain: case series of 10 patients and review of the literature. *Medicine (Baltimore)* 93(3):121-134, 2014.

[47] Cai FZ, Lester S, Lu T et al. Mild autonomic dysfunction in primary Sjögren's syndrome: a controlled study. *Arthritis Res Ther* 10(2):R31, 2008.

[48] Scofield RH. Vasculitis in Sjögren's syndrome. *Curr Rheumatol Rep* 13(6):482-488, 2011.

[49] Ferri C, Mascia MT: Cryoglobulinemic vasculitis. *Curr Opin Rheumatol* 18(1):54–63, 2006.

[50] Bartoloni E, Baldini C, Schillaci G et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicenter cohort study. *J Intern Med* 278(2):185-192, 2015.

[51] Horvath IF, Szodoray P, Zeher M. Primary Sjögren's syndrome in men: clinical and immunological characteristic based on a large cohort of Hungarian patients. *Clin Rheumatol* 27(12):1479-1483, 2008.

[52]

Mathews PM, Hahn S, Hessen M et al. Ocular complications of primary Sjögren syndrome in men. *Am J Ophthalmol* 160(3):447-452, 2015.

[53] Molina R, Provost TT, Arnett FC et al. Primary Sjögren's syndrome in men. Clinical, serologic, and immunogenetic features. *Am J Med* 80(1):23-31, 1986.

[54] Drosos AA, Tsiakou EK, Tsifetaki N et al. Subgroups of primary Sjögren's syndrome in male and paediatric Greek patients. *Ann Rheum Dis* 56(5):333-335, 1997.

[55] Díaz-López C, Geli C, Corominas H et al. Are there clinical or serological differences between male and female patients with primary Sjögren's syndrome? *J Rheumatol* 31(7):1352-1355, 2004.

[56] Baer AN, McAdams DeMarco M, Shiboski SC et al. The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjögren's syndrome. *Ann Rheum Dis* 74(8):1557-1561, 2015.

[57] Shiboski CH, Shiboski SC, Seror R et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 69(1):35-45, 2017.

[58] Suresh L, Malyavantham K, Shen L et al. Investigation of novel autoantibodies in Sjogren's syndrome utilizing sera from the Sjogren's international collaborative clinical alliance cohort. *BMC Ophthalmol* 15:38, 2015.

[59] Movva S, Carsons S. Review of pediatric Sjögren's syndrome. *Pediatr Allergy Immunol Pulmonol* 27(3):111-114, 2014.

[60] Lieberman SM. Childhood Sjögren's syndrome: insights from adults and animal models. *Curr Opin Rheumatol* 25(5):651-657, 2013.

[61] Mehta J, Lieberman S. Childhood Sjogren's. *Sjogren's Quarterly* 11(1):1,2,4,5, 2016.

[62] Kovács L, Marczinovits I, György A, et al: Clinical associations of autoantibodies to human muscarinic acetylcholine receptor 3(213–228) in primary Sjogren's syndrome. *Rheumatology (Oxford)* 44(8):1021–1025, 2005.

[63] Hansen A, Lipsky PE, Dorner T: B cells in Sjögren's syndrome: indications for disturbed selection and differentiation in ectopic lymphoid tissue. *Arthritis Res Ther* 9(4):218, 2007.

[64] Vitali C, Bombardieri S, Jonsson R, et al: Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 61(6):554–558, 2002.

[65] Daniels TE: Labial salivary gland biopsy in Sjogren's syndrome. Assessment as a diagnostic criterion in 362 suspected cases. *Arthritis Rheum* 27(2):147–156, 1984.

[66] Pijpe J, Kalk WW, van der Wal JE, et al: Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjogren's syndrome. *Rheumatology (Oxford)* 46(2):335–341, 2007.

[67] Pollard RP, Pijpe J, Bootsma H, et al: Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study. *J Rheumatol* 38(10):2198–2208, 2011.

[68] Blatt IM, French AJ, Holt JF, et al: Secretory sialography in diseases of the major salivary glands. *Ann Otol Rhinol Laryngol* 65(2):295–317, 1956.

[69] Blatt IM: On sialectasis and benign lymphosialdenopathy. (The pyogenic parotitis, gougerot-Sjoegren's syndrome, Mikulicz's disease complex.) A ten-year study. *Laryngoscope* 74:1684–1746, 1964.

[70] Hermann GA, Vivino FB, Goin JE: Scintigraphic features of chronic sialadenitis and Sjogren's syndrome: a comparison. *Nucl Med Commun* 20(12):1123–1132, 1999.

[71] Takagi Y, Kimura Y, Nakamura H, et al: Salivary gland ultrasonography: can it be an alternative to sialography as an imaging modality for Sjogren's syndrome? *Ann Rheum Dis* 69(7):1321–1324, 2010.

[72] Tzioufas AG, Mitsias DI, Moutsopoulos HM: Sjogren syndrome. In Hochberg MC, Silman AJ, editors: Rheumatology, Philadelphia, 2008, Elsevier, pp 1348–1349.

[73] Pennell LM, Galligan CL, Fish EN: Sex affects immunity. *J Autoimmun* 38(2-3):J282-291, 2012.

[74] Valtysdottir ST, Wide L, Hallgren R: Low serum dehydroepiandrosterone sulfate in women with primary Sjögren's syndrome as an isolated sign of impaired HPA axis function. *J Rheumatol* 28(6):1259–1265, 2001.

[75] Sullivan DA, Belanger A, Cermak JM, et al: Are women with Sjögren's syndrome androgen-deficient? *J Rheumatol* 30(11):2413–2419, 2003.

[76] Hartkamp A, Geenen R, Godaert GL, et al: Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. *Ann Rheum Dis* 67(1):91–97, 2008.

[77] Manoussakis MN, Georgopoulou C, Zintzaras E, et al: Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. *Arthritis Rheum* 50(3):882–891, 2004.

[78] Xu D, Tian X, Zhang W, et al: Sjogren's syndrome-onset lupus patients have distinctive clinical manifestations and benign prognosis: a case-control study. *Lupus* 19(2):197–200, 2010.

[79] Baer AN, Maynard JW, Shaikh F, et al: Secondary Sjogren's syndrome in systemic lupus erythematosus defines a distinct disease subset. *J Rheumatol* 37(6):1143–1149, 2010.

[80] Vitali C, Palombi G, Baldini C, et al: Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum* 56(7):2223–2231, 2007.

[81] Hu S, Gao K, Pollard R, et al: Preclinical validation of salivary biomarkers for primary Sjögren's syndrome. *Arthritis Care Res (Hoboken)* 62(11):1633–1638, 2010.

[82]Seror R, Ravaud P, Bowman SJ, et al: EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis* 69(6):1103–1109, 2010.

[83] Seror R, Ravaud P, Mariette X, et al: EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. *Ann Rheum Dis* 70(6):968–972, 2011.

[84] Seror R, Theander E, Brun JG, et al. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 74(5):859-866, 2015.

[85] Seror R, Theander E, Bootsma H et al. Outcome measures for primary Sjögren's syndrome: a comprehensive review. *J Autoimmun* 51:51-56, 2014.

[86] Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al: Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 81(4):270–280, 2002.

[87] Asmussen K, Andersen V, Bendixen G, et al: A new model for classification of disease manifestations in primary Sjögren's syndrome: evaluation in a retrospective long-term study. *J Intern Med* 239(6):475–482, 1996.

[88] Zufferey P, Meyer OC, Grossin M, et al: Primary Sjögren's syndrome (SS) and malignant lymphoma. A retrospective cohort study of 55 patients with SS. *Scand J Rheumatol* 24(6):342–345, 1995.

[89] Vissink A, Kalk WW, Mansour K, et al: Comparison of lacrimal and salivary gland involvement in Sjögren's syndrome. *Arch Otolaryngol Head Neck Surg* 129(9):966–971, 2003.