eMedicine Specialties > Dermatology > Connective Tissue Diseases

Sjogren Syndrome

Robert A Schwartz, MD, MPH, Professor and Head, Dermatology, Professor of Pathology, Pediatrics, Medicine, and Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School **Joanna Narbutt, MD, PhD,** Senior Registrar, Lecturer, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Anna Zalewska, MD, PhD,** Assistant Professor, Adjunct Professor, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Anna Sysa-Jedrzejowska, MD, PhD,** Head, Professor, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Jolanta Dorota Torzecka, MD, PhD,** Consulting Staff, Department of Dermatology and Venereology, Medical University of Lodz, Poland

Updated: Aug 31, 2009

Introduction

Background

Sjögren syndrome (SS) is a chronic systemic disorder characterized by polyglandular tissue destruction that causes keratoconjunctivitis sicca (KCS) and xerostomia. Patients with primary Sjögren syndrome have keratoconjunctivitis sicca and xerostomia, whereas those with secondary Sjögren syndrome have keratoconjunctivitis sicca, xerostomia, and an autoimmune disease. Most commonly, this autoimmune disease is rheumatoid arthritis (RA); however, it can also be systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective-tissue disease (MCTD), or subacute cutaneous lupus erythematosus (SCLE).

In addition to primary Sjögren syndrome and secondary Sjögren syndrome, juvenile Sjögren syndrome is another subtype. Some patients with lacrimal gland enlargement resulting from lymphocytic infiltration may represent a new subtype of primary Sjögren syndrome.[1]

Pathophysiology

Sjögren syndrome is caused by certain factors that lead to autoimmune dysregulation, which results in the destruction of the acinar cells and ductal epithelia with subsequent dry eyes and dry mouth. In patients with autoimmune diseases, activated lymphocytes selectively migrate into the lacrimal and salivary glands, leading to tissue damage.

Antimuscarinic antibodies in primary Sjögren syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. A clearly defined pathogenic autoantibody has not been identified, although autoantibodies that bind to the muscarinic M(3) receptors (M(3)R), which regulate fluid secretion in salivary glands, have been proposed. One recent study showed that immunoglobulin G (IgG) antimuscarinic antibodies in primary Sjögren syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells.[2]

The etiology and pathophysiology of Sjögren syndrome are still unknown. Autoimmunologic factors and a genetic predisposition are associated with Sjögren syndrome. The following human leukocyte antigens (HLAs) increase the risk of Sjögren syndrome: DRB1, DRB3, DR5, DRw11, DR52, DRw53, DQA1*0501, DQB1*0201, and DQB1*0301. A

strong association between Sjögren syndrome and HLA-DR3 is observed. The frequency of HLA-DR52 in patients with primary Sjögren syndrome is estimated to be 87%, but it is also significantly increased in secondary Sjögren syndrome that occurs with rheumatoid arthritis or systemic lupus erythematosus. Anti-Ro/SS-A and anti-La/SS-B antibodies are strongly associated with HLA-DR2 and HLA-DR3. (The latter is a correlate of the severity of the disease rather than a predisposing factor.) Polymorphism of the mannose-binding lectin gene seems to be one of the genetic factors that determines an individual's susceptibility to Sjögren syndrome.
Viral infection could be involved in the induction of Sjögren syndrome. Epstein-Barr virus (EBV), human T-lymphotrophic virus 1 (HTLV-1), human herpesvirus 6 (HHV-6), human immunodeficiency virus 1 (HIV-1), hepatitis C virus (HCV), and cytomegalovirus (CMV) may have a role.

Polyclonal B-lymphocyte hyperreactivity is one of the most important immunologic phenomena. It results in hypergammaglobulinemia and the presence of the following immune complexes and various antibodies: anti-Ro/SS-A, anti-La/SS-B (95%), rhalvato da Windows Internet Explorer 8> Subject: Sjogren Syndrome: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:47:05 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_01A5_01CA2CF9.399D9D30" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_01A5_01CA2CF9.399D9D30 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1066649-print

eMedicine Specialties > Dermatology > Connective Tissue Diseases

Sjogren Syndrome

Robert A Schwartz, MD, MPH, Professor and Head, Dermatology, Professor of Pathology, Pediatrics, Medicine, and Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School
Joanna Narbutt, MD, PhD, Senior Registrar, Lecturer, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Anna Zalewska, MD, PhD,** Assistant Professor, Adjunct Professor, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Anna Sysa-Jedrzejowska, MD, PhD,** Head, Professor, Department of Dermatology and Venereology, Medical University of Lodz, Poland; **Jolanta Dorota Torzecka, MD, PhD,** Consulting Staff, Department of Dermatology and Venereology, Medical University of Lodz, Poland

Updated: Aug 31, 2009

Introduction

Background

Sjögren syndrome (SS) is a chronic systemic disorder characterized by polyglandular tissue destruction that causes keratoconjunctivitis sicca (KCS) and xerostomia. Patients with primary Sjögren syndrome have keratoconjunctivitis sicca and xerostomia, whereas those with secondary Sjögren syndrome have keratoconjunctivitis sicca, xerostomia, and an autoimmune disease. Most commonly, this autoimmune disease is rheumatoid arthritis (RA); however, it can also be systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective-tissue disease (MCTD), or subacute cutaneous lupus erythematosus (SCLE).

In addition to primary Sjögren syndrome and secondary Sjögren syndrome, juvenile Sjögren syndrome is another subtype. Some patients with lacrimal gland enlargement resulting from lymphocytic infiltration may represent a new subtype of primary Sjögren syndrome.[1]

Pathophysiology

Sjögren syndrome is caused by certain factors that lead to autoimmune dysregulation, which results in the destruction of the acinar cells and ductal epithelia with subsequent dry eyes and dry mouth. In patients with autoimmune diseases, activated lymphocytes selectively migrate into the lacrimal and salivary glands, leading to tissue damage.

Antimuscarinic antibodies in primary Sjögren syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. A clearly defined pathogenic autoantibody has not been identified, although autoantibodies that bind to the muscarinic M(3) receptors (M(3)R), which regulate fluid secretion in salivary glands, have been proposed. One recent study showed that immunoglobulin G (IgG) antimuscarinic antibodies in primary Sjögren syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells.[2]

The etiology and pathophysiology of Sjögren syndrome are still unknown. Autoimmunologic factors and a genetic predisposition are associated with Sjögren syndrome. The following human leukocyte antigens (HLAs) increase the risk of Sjögren syndrome: DRB1, DRB3, DR5, DRw11, DR52, DRw53, DQA1*0501, DQB1*0201, and DQB1*0301. A strong association between Sjögren syndrome and HLA-DR3 is observed. The frequency of HLA-DR52 in patients with primary Sjögren syndrome is estimated to be 87%, but it is also significantly increased in secondary Sjögren syndrome that occurs with rheumatoid arthritis or systemic lupus erythematosus. Anti-Ro/SS-A and anti-La/SS-B antibodies are strongly associated with HLA-DR2 and HLA-DR3. (The latter is a correlate of the severity of the disease rather than a predisposing factor.)
Polymorphism of the mannose-binding lectin gene seems to be one of the genetic factors that determines an individual's susceptibility to Sjögren syndrome.
Viral infection could be involved in the induction of Sjögren syndrome. Epstein-Barr virus (EBV), human T-lymphotrophic virus 1 (HTLV-1), human herpesvirus 6 (HHV-6), human immunodeficiency virus 1 (HIV-1), hepatitis C virus (HCV), and cytomegalovirus (CMV) may have a role.

Polyclonal B-lymphocyte hyperreactivity is one of the most important immunologic phenomena. It results in hypergammaglobulinemia and the presence of the following immune complexes and various antibodies: anti-Ro/SS-A, anti-La/SS-B (95%), rheumatoid factor, antithyroglobulin antibodies (25%), antimicrosomal antibodies, histone antibodies (occasionally), anti-U4/U6snRNP-specific antibodies (uniquely), autoantibodies against platelet GPIIb-IIIa complex, anti-ssDNA antibodies, cryoglobulins, both cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies (ANCA), and precipitating antibodies to extracts of lacrimal and salivary glands.

An autoimmune etiology also is proven by the occurrence of a Sjögren syndrome-type syndrome after allogenic bone marrow transplantation. A selective defect in aquaporin-5 is suggested to contribute to decreased lacrimation and dry eyes in patients with Sjögren syndrome. An anti–120-kd alpha-fodrin immune response plays a critical role in the development of primary Sjögren syndrome. Alpha-fodrin proteolysis and tissue destruction are due to apoptosis, activated by EBV infection, among other causes.

Proapoptotic molecules Bax and caspase 3 are overexpressed in the salivary gland epithelial cells. Intense B lymphocyte infiltration (20-25%) and $CD4^+$ T-cell infiltration (70-80%) localized in the salivary glands leads to the destruction of epithelial cells. The role of various cytokines, such as tumor necrosis factor-alpha, is also considered in the development of Sjögren syndrome. High expression of the intercellular adhesion molecule 1 (ICAM-1) by the salivary epithelium in patients with Sjögren syndrome suggests that it has an important role in the pathogenesis of the disease.

Sex may influence the immunologic manifestations of primary Sjögren syndrome. The prevalence of serologic markers tends to be lower in male patients than in female patients. The role of sex hormones (eg, estrogens, androgens) in the pathogenesis of primary Sjögren syndrome remains unknown, although adrenal and gonadal steroid hormone deficiency probably affects the immune function of the organism.

The titers of anti-Ro and anti-La antibodies are correlated with the severity of the disease and the presence of extraglandular manifestations of Sjögren syndrome. These autoantibodies are often present in other diseases, especially subacute cutaneous lupus erythematosus. Anti-Ro antibodies are particularly associated with vasculitis, purpura, lymphadenopathy, and hematologic abnormalities (eg, thrombocytopenia, anemia,

lymphopenia). Although the clinical relevance of anti-Ro and anti-La antibodies is obvious, their immunopathogenic role is not fully elucidated. The pathogenesis of juvenile Sjögren syndrome seems to be the same as that of adult Sjögren syndrome.

Frequency

United States

The prevalence is 4 cases per 100,000 population. A 2008 US Centers for Disease Control and Prevention study estimates that Sjögren syndrome affects 0.4-3.1 million American adults.[3]

International

Approximately 1-3% of the general population is affected. Sjögren syndrome is often underdiagnosed.

Mortality/Morbidity

- The prognosis with Sjögren syndrome is generally better than that of other autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis).
- Death occurs, especially in secondary Sjögren syndrome and in cases with myelopathy.
- To the authors' knowledge, no data are available regarding mortality and morbidity rates in persons with Sjögren syndrome.

Race

No racial predilection is recognized.

Sex

Women are affected more often than men; the female-to-male ratio is 9:1.

Age

Sjögren syndrome may occur in persons of any age, but it usually occurs in persons aged 30-50 years. The disease rarely affects children.

Clinical

History

The clinical presentation of Sjögren syndrome may vary. The onset is insidious. It usually starts in women aged 40-60 years, but it also can affect men and children. The first symptoms in primary Sjögren syndrome can be easily overlooked or misinterpreted, and diagnosis can be delayed for as long as several years.

Xerophthalmia and xerostomia are the main clinical presentations in adults. Bilateral parotid swelling is the most common sign of onset in children. Symptoms of Sjögren syndrome can decrease the patient's quality of life in terms of its physical, psychological, and social aspects. Sjögren syndrome is diagnosed on the basis of either European or San Diego classification criteria.

- European classification
    - Ocular symptoms - Positive response to 1 of 3 questions pertaining to dry eyes
    - Ocular signs - Positive Schirmer test (<5 mm in 5 min) or positive rose bengal staining
    - Oral symptoms - Positive response to 1 of 3 questions pertaining to dry mouth

    - Salivary gland involvement - Objective evidence of salivary gland involvement; salivary scintigraphy; parotid sialography; unstimulated salivary flow less than 1.5 mm/min
    - Serologic or autoantibody test results - Presence of autoantibodies to Ro (SS-A), La (SS-B), or both
    - Categories
        - Primary Sjögren syndrome - Presence of any of 4 of the previous 6 categories
        - Secondary Sjögren syndrome - Presence of potentially associated connective tissue or autoimmune disease with the first 2 categories (ocular symptoms and ocular signs) plus any 2 of the next 3 categories
- San Diego classification
    - Ocular symptoms - Symptoms of ocular dryness
    - Ocular signs - Positive Schirmer test (<8 mm in 5 min) and positive rose bengal staining of the cornea
    - Oral symptoms - Symptoms of oral dryness
    - Histopathologic findings - Abnormal biopsy findings in a minor salivary gland (focus score >2 in an average of 4 lobules, multiple foci of lymphoid inflammation)
    - Salivary gland involvement - Decreased parotid flow rate (eg, Lashley cups)
    - Serologic or autoantibody test results - Serologic evidence of systemic autoimmunity, rheumatoid factor greater than 1:320 or antinuclear antibody (ANA) level greater than 1:320 or positive result for SS-A (Ro) or SS-B (La) antibodies
    - Categories
        - Definite - Objective evidence of dry eyes and/or mouth, autoantibody presence, and characteristic results from minor salivary gland biopsy
        - Probable - Same as the above, but results from minor salivary gland biopsy not required
        - Primary Sjögren syndrome - Characteristic signs and symptoms (above) without associated autoimmune disease
        - Secondary Sjögren syndrome - Same as primary Sjögren syndrome plus the presence of rheumatoid factor, systemic lupus erythematosus, polymyositis, scleroderma, or biliary cirrhosis
- Patients with T-cell ($CD3^+$), large, granular lymphocyte leukemia have a high prevalence of autoantibodies and associated autoimmune diseases, including syndromes, which is an important but often underrecognized association.[4]

Physical

Secondary Sjögren syndrome appears late in the course of the primary disease. However, in some patients, primary Sjögren syndrome may precede systemic lupus erythematosus by many years. Secondary Sjögren syndrome is usually mild, and sicca symptoms are the main feature. Unlike those with primary Sjögren syndrome, patients with the secondary type have significantly fewer systemic manifestations. These manifestations include salivary gland swelling, lung involvement, nervous system involvement, renal involvement, Raynaud phenomenon, and lymphoproliferative disorders. In secondary Sjögren syndrome, symptoms of the primary disease predominate. Secondary Sjögren syndrome does not modify the prognosis or outcome of the basic disease.

The physical symptoms of primary Sjögren syndrome can be divided into glandular and extraglandular symptoms.

- Glandular symptoms
    - Ocular
        - Keratoconjunctivitis sicca or dry eye syndrome, characterized by chronic dryness of the cornea and conjunctiva
        - Discomfort (eg, irritation, pain, redness, burning, itching, foreign body sensation, photophobia, blurred vision)
    - Mouth
        - Dryness
        - Tongue - Red, smooth, and dry
        - Dental caries - Severe and progressive
        - Parotid duct narrowing
        - Lips - Red, dry, and scaly
        - Cracks at the corners of the mouth

        - Chronic oral candidiasis
        - Periodontal conditions: These were evaluated in Sjögren syndrome patients, and Sjögren syndrome appears to negatively affect the periodontal condition. Gingival inflammation was more evident in the individuals with Sjögren syndrome, particularly those with secondary Sjögren syndrome.[5]
        - Recurrent swelling of the parotid glands (22-66% of patients), sometimes also submaxillary and sublingual glands
    - Other mucous membranes
        - Atrophic changes in the mucous membranes of the upper respiratory tract leading to nasal dryness, recurrent infections, hoarseness, and aphonia
        - Atrophic rhinitis
        - Atrophic changes in the vulva and vagina resulting in pruritus and vaginitis
        - Dryness of the anal and rectal mucous membranes (eg, pruritus, inflammation)
    - Skin
        - Dryness of the skin occurs in 50% of patients with Sjögren syndrome; scaling occurs in about 25% of patients. The skin may be irritable with secondary lichenification.
        - Partial or complete loss of sweating may be present.
        - Hair may be dry, sparse, and brittle; diffuse alopecia may involve the scalp, limbs, axillae, or pubis.
        - Nail folds may show capillaroscopic abnormalities, which are associated with the presence of antiendothelial cell antibodies.[6]
        - Erythema of the nose and cheeks may be present.
        - Annular erythematous rash with scales, localized especially on the face and neck, is recognized as a cutaneous manifestation of Sjögren syndrome. The lesions are recurrent and clear without pigmentation; no photosensitivity is observed.
        - A higher risk of cutaneous vasculitis is noted.
        - In Japanese patients with Sjögren syndrome, annular erythema is divided into 3 types: Sweet disease–like annular erythema with an elevated border, subacute cutaneous lupus erythematosus–like marginally scaled erythema, and papular erythema. These lesions bear some clinical similarities to the annular lesions of subacute cutaneous lupus erythematosus, but their histopathologic features are distinct from those of subacute cutaneous lupus erythematosus. Significant mucin depositions are observed.
        - Sjögren vasculitis involves postcapillary venules, typically on the lower legs. These patients were formerly classified as having Waldenström hypergammaglobulinemic purpura.
- Extraglandular symptoms
    - Gastrointestinal tract
        - Esophageal motility abnormalities
        - Pancreatic involvement
        - Splenomegaly
        - Digestive symptoms (due to atrophy of the gastric mucous membrane with achlorhydria)
        - Hepatitis (13%)
    - Lungs[7]: Pulmonary abnormalities occur in 9-29% of cases; they are similar in both primary and secondary Sjögren syndrome.
        - Pulmonary fibrosis
        - Pulmonary hypertension
        - Recurrent chest infections
        - Granulomatous infiltration and fibrosing alveolitis
        - Restrictive ventilatory defect
        - Impaired gas transfer
    - Articular changes (eg, arthritis): These occur in 42% of patients with Sjögren syndrome.
    - Urinary tract: Patients with Sjögren syndrome have significantly more urinary problems than those without Sjögren syndrome.
        - Symptoms of an irritated bladder
        - Urinary frequency and suprapubic pain

        - Renal tubular dysfunction: Patients with primary Sjögren syndrome commonly are first seen because of renal impairment, usually from renal tubular dysfunction.[8]
        - Renal tubular acidosis: This affects one third of patients with Sjögren syndrome. A correlation apparently exists between hypergammaglobulinemia and distal renal tubular acidosis.[8]
        - Interstitial nephritis (This is rare; occurs in 4% of cases; and is often accompanied by cryoglobulinemia, a decreased level of complement, and the presence of circulating immune complexes.)
        - Impaired renal concentrating ability, generalized aminoaciduria
    - Nervous system
        - A combination of lesions and relapses can suggest multiple sclerosis. Myelopathy rarely occurs in the course of primary Sjögren syndrome. It appears as Brown-Séquard syndrome, acute transverse myelitis, or progressive myelopathy. Clinically, cases with nervous system involvement present with paraparesis or paraplegia resulting from lesions at the thoracic or cervicothoracic levels.
        - Peripheral neuropathy occurs in 10-35% patients with primary Sjögren syndrome. Peripheral nerve dysfunction may occur; this can include trigeminal sensory neuropathy, mononeuropathy multiplex, distal sensorimotor polyneuropathy, or pure sensory neuropathy. This tends to be a small-fiber peripheral neuropathy.[9] Painful distal paresthesias in the feet may be evident, as may abnormal sweating. Examination may reveal findings that include decreased pinprick sensation.
        - Isolated cranial nerve involvement rarely occurs in primary Sjögren syndrome.
        - Central nervous system involvement is less common (10-25% of patients with Sjögren syndrome) than other types of involvement. It ranges from neuropathy, hemiparesis, transverse myelitis, and dystonia to even encephalopathy and dementia.
        - In Sjögren syndrome, focal brain lesions can be present in the cerebral white matter.
        - Dysregulation of hypothalamic-pituitary-adrenal and thyroid axes can cause some neurologic disturbances.

Causes

The following are causes of Sjögren syndrome.

- Genetic factors
    - The presence of HLA-DRB1, HLA-DRB3, HLA-DR5, HLA-DRw11, HLA-DR52, HLA-DRw53, and other HLAs increase the risk of Sjögren syndrome.
    - Polymorphism of the mannose-binding lectin gene is likely to be one of the genetic factors that determines an individual's susceptibility to Sjögren syndrome.
- Viral infections
    - Epstein-Barr virus
    - HTLV-1 and HIV-1
    - Human herpesvirus 6
    - Hepatitis C virus
    - Cytomegalovirus
- Autoimmune dysregulation (loss of immune tolerance and production of various autoantibodies, eg, ANA, anti-Ro, anti-La)
- Dysregulation of apoptosis
- Adrenal and gonadal steroid hormone deficiency

Differential Diagnoses

Amyloidosis, Primary Systemic

Sarcoidosis

Other Problems to Be Considered

Xerophthalmia, xerostomia, and enlargement of the parotid glands can result from adverse effects of drugs and other diseases.

Sjögren syndrome (SS) can be underdiagnosed or misdiagnosed. Histologic findings of the following can be consistent with Sjögren syndrome: sarcoidosis, graft-versus-host disease, HIV infection, HTLV-1 infection, HCV infection, and keratoconjunctivitis sicca.

Systemic lupus erythematosus might be considered, especially at onset of the disease.
Autoimmune thyroid dysfunction may be present.

HIV infection can result in diffuse infiltrative lymphocytosis syndrome (DILS), which is characterized by parotid enlargement; involvement of the renal, lung, and gastrointestinal systems; and a low frequency of autoantibody presence.

Chronic graft versus host disease may mimic symptoms associated with idiopathic Sjögren syndrome.[10]

Workup

Laboratory Studies

- Some laboratory tests can be used to assess salivary and lacrimal involvement in Sjögren syndrome.
    - However, no single test is sufficiently sensitive or specific in diagnosing Sjögren syndrome.
    - Sjögren syndrome is properly diagnosed only when the results of various tests are simultaneously positive and when subjective symptoms and serologic abnormalities are present.
- Laboratory test results may indicate the following:
    - Elevated erythrocyte sedimentation rate (ESR)
    - Anemia
    - Leukopenia
    - Eosinophilia
    - Hypergammaglobulinemia
    - Presence of antinuclear antibodies, especially anti-Ro and anti-La
    - Presence of rheumatoid factor
    - Presence of anti–alpha-fodrin antibody (reliable diagnostic marker of juvenile Sjögren syndrome)
- Atypical autoantibodies in 82 patients with primary Sjögren syndrome were evaluated.[11] An immunological overlap (defined by the presence of autoantibodies typical of other systemic autoimmune diseases) was evident in 20% of patients with primary Sjögren syndrome. The clinical significance of these atypical autoantibodies varied widely.

Imaging Studies

- For the assessment of salivary gland involvement, the following imaging studies are used:
    - Parotid sialography
    - Salivary gland scintigraphy[12]
    - Ultrasonography of salivary gland[13]
    - Magnetic resonance (MR) sialography
- Dynamic contrast-enhanced MR imaging may be valuable to quantify microvascular function in persons with Sjögren syndrome and to differentiate between patients with and those without Sjögren syndrome.[14]

Other Tests

- The diagnosis of Sjögren syndrome is difficult because no good diagnostic test is available; excluding an underlying disease is important.
- Tests that may be helpful in the diagnosis include the following:
    - Schirmer test for assessment of eye function (positive when result is <5 mm)

- Rose bengal scoring for the assessment of the ocular involvement
- Minor salivary gland biopsy (widely used)
- Saliva collection from the mouth - Reduced basal and reflex lacrimation (basal lacrimation of 3 mm and stimulated lacrimation of 4 mm)
- Esophageal manometry for the assessment of esophageal motor function
- Electrophysiologic examination for the assessment of peripheral neuropathy

Histologic Findings

Histologic evaluation is valuable for diagnosing Sjögren syndrome and in ruling out other pathologic conditions (eg, amyloidosis, sarcoidosis, lymphoma, lipoproteinemia) with sicca manifestation. The histopathologic features of the labial salivary glands concerning the presence of focal lymphocytic sialadenitis in all or most of the glands in the specimen are of great importance in the diagnosis of Sjögren syndrome.

Focal lymphocytic sialadenitis (FLS) is defined as multiple, dense, aggregates of 50 or more lymphocytes (1 focus) in perivascular or periductal locations in the gland lobules. FLS is graded in terms of a focus score, which equals the number of foci divided by 4 mm^2. A score of greater than 1 focus per 4 mm^2 has a specificity of 83.5-95% and a sensitivity of 63-81.8% in the diagnosis of Sjögren syndrome. The focus score may be associated with keratoconjunctivitis sicca; presence of autoantibodies; and, less commonly, with xerostomia.

Besides these features, histologic examination may reveal dermal mucin deposition that resembles that of lupus erythematosus tumidus, the absence of sebaceous glands, and a decrease in the number of sweat glands. Cellular infiltration may be observed around the sweat glands. Degenerative changes in the apocrine glands and the external root sheath of hair are reported. Clinical symptoms seem to parallel the histologic changes; therefore, the results of sublabial minor salivary gland biopsy may be considered as markers of disease activity in patients with primary Sjögren syndrome.

In patients with a possible diagnosis of Sjögren syndrome but severe extraglandular symptoms, a lip biopsy is often performed to firmly establish the diagnosis of Sjögren syndrome. A 2007 study showed that not all patients undergoing lip biopsy derive diagnostic benefit from this procedure and that clinical symptoms and serology did not predict a positive lip biopsy.[15]

Treatment

Medical Care

No curative agents exist. The treatment of Sjögren syndrome (SS) is essentially symptomatic. In secondary Sjögren syndrome, treatment is based on the accompanying disease and its clinical features. Sjögren syndrome and associated systemic lupus erythematosus improve more than primary Sjögren syndrome. In Sjögren syndrome associated with polymyositis, monthly cyclophosphamide pulse therapy have been used successfully. In annular erythema in Japanese patients, prednisolone (10-20 mg/d) is effective.

New therapeutic strategies designed to facilitate AQP5 trafficking to the apical plasma membrane might prove useful for the management of dry eyes in Sjögren syndrome. The inhibition of protease activity in EBV-mediated apoptotic cells may be a potential therapeutic approach in the treatment of Sjögren syndrome.

Treatments and therapeutic agents for specific conditions may include the following:

- Dry eyes
    - Artificial tears (eg, methylcellulose, 1% hyaluronic acid solution, alcohol solutions) applied 4-6 times daily
    - Punctual occlusion with silicone plugs
    - Bromhexine 16 mg 3 times a day
    - Topical cyclosporine A 0.05-0.1% (reduces the lymphocyte infiltration of lacrimal glands)[16]
    - Ointments/oil-based drugs: The use of ointments and oil-based drugs are contraindicated.

    - Novel device: A novel device that promotes the release of meibomian sebum into the tear film by delivering latent heat to the eyelids can be used for dry eye patients with and without Sjögren syndrome to reduce symptoms.[17]
    - American Academy of Ophthalmology: The clinical guideline summary, Dry eye syndrome, may be helpful.[18]
- Dry mouth
    - Frequent small drinks and mouthwashes
    - Artificial saliva
    - Saliva stimulation (eg, by sweets, lemon drops)
    - Use of detergent-free toothpaste and topical use of fluoride
    - Potassium iodine and parasympathetic agents (eg, pilocarpine, neostigmine), bromhexine, trithioparamethoxyphenylpropene
    - Although not widely used, natural human interferon-alfa improves salivary output and decreases the incidence of xerostomia.
- Parotid enlargement
    - Nonsteroid anti-inflammatory drugs (NSAIDs), eg, naproxen
    - Low-dose corticosteroids, eg, prednisone
- Arthritis
    - NSAID, eg, naproxen
    - Low-dose corticosteroids, eg, prednisone
    - Chloroquine and hydroxychloroquine sulphate (not recommended by all the authors)
- Peripheral nerve dysfunction
    - No treatment is known.
    - Plasmapheresis is useful in patients with secondary neuropathy.
- Central nervous system involvement
    - Intravenous corticosteroids plus an immunosuppressive agent (eg, methylprednisolone and cyclophosphamide)
    - Plasmapheresis (Consider this in patients with sensory neuropathy associated with Sjögren syndrome.)
- Vasculitis - Immunosuppressive agents, if necessary
- Raynaud phenomenon - Pentoxifylline and nifedipine

Consultations

Consultations with the following specialists may be helpful:

- Rheumatologist
- Ophthalmologist
- Dentist
- Dermatologist
- Neurologist

Activity

Activity should be limited in patients with arthralgia.

Medication

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Authors report on the use of rituximab in primary Sjögren syndrome patients.[19,20,21]

Corticosteroids

These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli.

Prednisone (Deltasone, Orasone, Meticorten)

Immunosuppressant for treatment of autoimmune disorders. May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and also suppresses lymphocytes and antibody production and activity.

Dosing

Adult

5-60 mg/d PO qd or divided bid/qid; taper over 2 wk as symptoms resolve

Pediatric

4-5 mg/m^2/d PO; alternatively, 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve

Interactions

Coadministration with estrogens may decrease clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

Contraindications

Documented hypersensitivity; viral, fungal, connective tissue, or tubercular skin infections; peptic ulcer disease; hepatic dysfunction; GI disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use

Immunosuppressant agents

These agents inhibit cell growth and proliferation, decreasing immune activity.

Cyclophosphamide (Cytoxan, Neosar)

Chemically related to nitrogen mustards. As an alkylating agent, the mechanism of action of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Rarely used in this condition because of its associated toxicity.

Dosing

Adult

500-750 mg/m^2 IV every mo

Pediatric

Administer as in adults

Interactions

Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; chloramphenicol may increase half-life while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase rate of metabolism and leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leukopenia and neuromuscular blockade by inhibiting cholinesterase activity

Contraindications

Documented hypersensitivity; severely depressed bone marrow function

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Regularly examine hematologic profile (particularly neutrophil and platelet counts) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis

Nonsteroidal anti-inflammatory agents

These agents have analgesic, anti-inflammatory, and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclo-oxygenase activity and prostaglandin synthesis. Other mechanisms may exist as well; these include inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation, and various cell membrane functions.

Naproxen (Anaprox, Naprosyn, Naprelan)

For relief of mild to moderate pain; inhibits inflammatory reactions and pain by decreasing activity of cyclo-oxygenase and thereby decreasing prostaglandin synthesis.

Dosing

Adult

500 mg PO followed by 250 mg PO q6-8h; not to exceed 1.25 g/d

Pediatric

<2 years: Not established
>2 years: 2.5 mg/kg/dose PO; not to exceed 10 mg/kg/d

Interactions

Coadministration with aspirin increases risk of inducing serious NSAID-related adverse effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT with anticoagulant use (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; may increase phenytoin levels when administered concurrently

Contraindications

Documented hypersensitivity; peptic ulcer disease; recent GI bleeding or perforation; renal insufficiency

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Category D in third trimester of pregnancy; acute renal insufficiency, interstitial nephritis, hyperkalemia, hyponatremia, and renal papillary necrosis may occur; patients with preexisting renal disease or compromised renal perfusion have a risk of acute renal failure; leukopenia occurs rarely, is transient, and usually returns to normal during therapy; persistent leukopenia, granulocytopenia, or thrombocytopenia warrants further evaluation and may require discontinuation of drug

Antimalarial agents

Certain types of agents in this class have anti-inflammatory activity.

Chloroquine phosphate (Aralen Phosphate)

Anti-inflammatory activity; suppresses lymphocyte transformation and may have a photoprotective effect.

Dosing

Adult

Lupus: 250 mg PO qd

Pediatric

Not established

Interactions

Cimetidine may increase serum levels (and possibly that of other 4-aminoquinolones); magnesium trisilicate may decrease absorption of 4-aminoquinolones

Contraindications

Documented hypersensitivity; psoriasis, retinal and visual field changes attributable to 4-aminoquinolones

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in hepatic disease, G-6-PD deficiency, psoriasis, and porphyria; not recommended for long-term use in children; perform periodic ophthalmologic examinations; test for muscle weakness; retinopathy, tinnitus, nerve deafness, skin eruption, headache, anorexia, nausea, vomiting, and diarrhea may occur

Immune globulin intravenous

These agents are used to improve the clinical and immunologic aspects of the disease. They may decrease autoantibody production and increase the solubilization and removal of immune complexes.

Immune globulin intravenous (Gamimune, Gammagard, Sandoglobulin, Gammar-P)

Neutralizes circulating myelin antibodies by means of anti-idiotypic antibodies. Down-regulates proinflammatory cytokines, including INF-gamma. Blocks Fc receptors on macrophages. Suppresses inducer T and B cells and augments suppressor T cells. Blocks complement cascade; promotes remyelination; may increase CSF IgG (10%).

Dosing

Adult

2 g/kg IV over 2-5 d

Pediatric

Not established

Interactions

Increases toxicity of live-virus vaccine (MMR); do not administer within 3 mo of vaccine

Contraindications

Documented hypersensitivity; IgA deficiency; presence of anti-IgE and/or anti-IgG antibodies

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Check serum IgA before use (use IgA-depleted product, eg, Gammagard S/D); infusions may increase serum viscosity and thromboembolic events; infusions may increase risk of migraine attacks, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d after infusion); increases risk of renal tubular necrosis in elderly patients and in patients with diabetes, volume depletion, or preexisting kidney disease; associated changes in laboratory results include elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increase in ESR for 2-3 wk, and apparent hyponatremia

Lubricants

Lubricants are used to keep as much moisture in the eye as possible and to reduce irritation.

Artificial tears (Celluvisc, Murine, Refresh, Tears Naturale)

Contains equivalent of 0.9% NaCl and used to maintain ocular tonicity. Stabilizes and thickens precorneal tear film and prolongs tear film, which is short with dry eye states.

Dosing

Adult

1-2 gtt into affected eye tid/qid prn

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

A - Fetal risk not revealed in controlled studies in humans

Precautions

Hyperemia, photophobia, stickiness of eyelashes, or ocular discomfort or irritation may occur

Follow-up

Further Outpatient Care

- Sjögren syndrome (SS) patients should receive follow-up care by the specialists.

Complications

- Most complications result from concomitant connective tissue diseases.
- The occurrence of B-cell non-Hodgkin lymphoma (NHL) is the major complication in the course of disease in patients with Sjögren syndrome.
    - The risk of B-cell NHL is 44 times greater in patients with Sjögren syndrome than in a healthy population; NHL affects about 5% patients with Sjögren syndrome.
    - NHL occurs preferentially in the salivary glands and in other mucosa-associated lymphoid tissue. However, it can also occur in the lymph nodes or bone marrow.
- Corneal ulceration is a rare complication of Sjögren syndrome. It usually occurs secondary to rheumatoid arthritis.

Prognosis

- Sjögren syndrome is a chronic disease that usually has a mild course, but it may be complicated by NHL or severe systemic symptoms.
- Early diagnostic and therapeutic treatment of patients with primary Sjögren syndrome, together with close follow-up, may contribute to a significant improvement in their quality of life.[22]
- Brito-Zeron et al reported that exocrine gland involvement, vasculitis, hypocomplementemia, and the presence of cryoglobulins at diagnosis were features of a specific subset of primary Sjögren syndrome patients in whom more careful monitoring and more aggressive treatment is recommended.[23]

Patient Education

- Patients with Sjögren syndrome must be informed about the chronic nature of the illness and the goals of therapy.
- Patients with Sjögren syndrome should be aware of the possible coexistence of other potentially severe diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis.
- For excellent patient education resources, visit eMedicine's Arthritis Center. Also, see eMedicine's patient education article Sjögren Syndrome.

Miscellaneous

Medicolegal Pitfalls

- A negative biopsy result in the labial salivary glands or nasal mucosa does not exclude Sjögren syndrome.
- Potential effects of corticosteroid and cyclosporine A use should be taken into account when sublabial minor salivary gland biopsy results are interpreted.
- The risk of dental caries is increased in Sjögren syndrome; therefore, regular dental assessment is strongly advised.
- Chronic swelling and enlargement of the parotid glands may indicate the development of lymphoma. This possibility should be considered.
- Patients with severe lymphocytic infiltration in the minor salivary gland tissue rarely have kidney involvement. Often, they have lymphadenopathy and circulating rheumatoid factor, cryoglobulins, and anti-Ro/SS-A and anti-La/SS-B antibodies.
- Every patient requires a detailed examination to determine the extent and nature of the associated abnormalities.

Special Concerns

- Juvenile Sjögren syndrome should be considered in the differential diagnosis in children with recurrent parotitis, keratoconjunctivitis sicca, and pronounced and early tooth decay associated with xerostomia.
- Pregnancies in women with autoantibodies against Ro/SS-A and/or La/SS-B may be associated with a fetal atrioventricular (AV) block.
    - In high-risk pregnancies, the fetal heart rate must be monitored closely, especially from 16 weeks' gestation onward.
    - Dexamethasone treatment should be immediately started when a heart block is detected.

References

1. Parkin B, Chew JB, White VA, Garcia-Briones G, Chhanabhai M, Rootman J. Lymphocytic infiltration and enlargement of the lacrimal glands: a new subtype of primary Sjogren's syndrome?. *Ophthalmology*. Nov 2005;112(11):2040-7. [Medline].
2. Dawson LJ, Stanbury J, Venn N, Hasdimir B, Rogers SN, Smith PM. Antimuscarinic antibodies in primary Sjogren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. *Arthritis Rheum*. Apr 2006;54(4):1165-73. [Medline].
3. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. Jan 2008;58(1):15-25. [Medline].
4. Friedman J, Schattner A, Shvidel L, Berrebi A. Characterization of T-cell large granular lymphocyte leukemia associated with Sjogren's syndrome-an important but under-recognized association. *Semin Arthritis Rheum*. Apr 2006;35(5):306-11. [Medline].
5. Antoniazzi RP, Miranda LA, Zanatta FB, et al. Periodontal conditions of individuals with Sjogren's syndrome. *J Periodontol*. Mar 2009;80(3):429-35. [Medline].
6. Riccieri V, Sciarra I, Ceccarelli F, et al. Nailfold capillaroscopy abnormalities are associated with the presence of anti-endothelial cell antibodies in Sjogren's syndrome. *Rheumatology (Oxford)*. Jun 2009;48(6):704-6. [Medline].
7. Crestani B, Schneider S, Adle-Biassette H, Debray MP, Bonay M, Aubier M. [Respiratory manifestations during the course of Sjogren's syndrome]. *Rev Mal Respir*. Apr 2007;24(4 Pt 1):535-51. [Medline].
8. Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjogren's syndrome. *J Rheumatol*. Feb 2008;35(2):278-84. [Medline].
9. Lopate G, Pestronk A, Al-Lozi M, et al. Peripheral neuropathy in an outpatient cohort of patients with Sjogren's syndrome. *Muscle Nerve*. May 2006;33(5):672-6. [Medline].
10. Tuchocka-Piotrowska A, Puszczewicz M, Kolczewska A, Majewski D. [Graft-versus-host disease as the cause of symptoms mimicking Sjogren's syndrome]. *Ann Acad Med Stetin*. 2006;52 Suppl 2:89-93. [Medline].
11. Ramos-Casals M, Nardi N, Brito-Zeron P, et al. Atypical autoantibodies in patients with primary Sjogren syndrome: clinical characteristics and follow-up of 82 cases. *Semin Arthritis Rheum*. Apr 2006;35(5):312-21. [Medline].
12. Martinez-Lazaro R, Cortes-Blanco A, Velilla J. A pilot study of the salivary scintigraphy diagnostic performance in a Spanish population with Sjogren's syndrome diagnosed by the European criteria. *Ann Rheum Dis*. Mar 2001;60(3):302-3. [Medline].

13. Carotti M, Salaffi F, Manganelli P, Argalia G. Ultrasonography and colour doppler sonography of salivary glands in primary Sjogren's syndrome. *Clin Rheumatol*. 2001;20(3):213-9. [Medline].
14. Roberts C, Parker GJ, Rose CJ, et al. Glandular function in Sjogren syndrome: assessment with dynamic contrast-enhanced MR imaging and tracer kinetic modeling--initial experience. *Radiology*. Mar 2008;246(3):845-53. [Medline].
15. Langerman AJ, Blair EA, Sweiss NJ, Taxy JB. Utility of lip biopsy in the diagnosis and treatment of Sjogren's syndrome. *Laryngoscope*. Jun 2007;117(6):1004-8. [Medline].
16. Kunert KS, Tisdale AS, Stern ME, Smith JA, Gipson IK. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. *Arch Ophthalmol*. Nov 2000;118(11):1489-96. [Medline].
17. Spiteri A, Mitra M, Menon G, et al. Tear lipid layer thickness and ocular comfort with a novel device in dry eye patients with and without Sjogren's syndrome. *J Fr Ophtalmol*. Apr 2007;30(4):357-64. [Medline].
18. [Guideline] American Academy of Ophthalmology. American Academy of Ophthalmology Cornea/External Disease Panel, Preferred Practice Patterns Committee. Dry eye syndrome. *National Guidelines Clearinghouse*. 2008.
19. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. *Ann Rheum Dis*. Nov 2008;67(11):1541-4. [Medline].
20. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. *Arthritis Rheum*. Sep 2005;52(9):2740-50. [Medline].
21. Meijer JM, Pijpe J, Vissink A, Kallenberg CG, Bootsma H. Treatment of primary Sjogren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. *Ann Rheum Dis*. Feb 2009;68(2):284-5. [Medline].
22. Belenguer R, Ramos-Casals M, Brito-Zeron P, et al. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjogren's syndrome. *Clin Exp Rheumatol*. May-Jun 2005;23(3):351-6. [Medline].
23. Brito-Zeron P, Ramos-Casals M. [Prognosis of patients with primary Sjogren's syndrome]. *Med Clin (Barc)*. Feb 2 2008;130(3):109-15. [Medline].
24. Andres E, Federici L, Sibilia J. Myelopathy in Sjogren's syndrome: a causative role for cobalamin (vitamin B12) deficiency. *Drugs*. 2006;66(5):729. [Medline].
25. Bolstad AI, Wassmuth R, Haga HJ, Jonsson R. HLA markers and clinical characteristics in Caucasians with primary Sjogren's syndrome. *J Rheumatol*. Jul 2001;28(7):1554-62. [Medline].
26. de Seze J, Delalande S, Fauchais AL, et al. Myelopathies secondary to Sjogren's syndrome: treatment with monthly intravenous cyclophosphamide associated with corticosteroids. *J Rheumatol*. Apr 2006;33(4):709-11. [Medline].
27. Esch TR. Pathogenetic factors in Sjogren's syndrome: recent developments. *Crit Rev Oral Biol Med*. 2001;12(3):244-51. [Medline].
28. Fox RI, Michelson P, Casiano CA, Hayashi J, Stern M. Sjogren's syndrome. *Clin Dermatol*. Sep-Oct 2000;18(5):589-600. [Medline].
29. Fujimura T, Aiba S, Suetake T, Tagami H. Erythematous swelling of the lip associated with Sjogren's syndrome and mimicking cheilitis granulomatosa. *J Dermatol*. Jan 2001;28(1):47-9. [Medline].
30. Gasparotto D, De Vita S, De Re V, et al. Extrasalivary lymphoma development in Sjogren's syndrome: clonal evolution from parotid gland lymphoproliferation and role of local triggering. *Arthritis Rheum*. Nov 2003;48(11):3181-6. [Medline].
31. Haimowitz JE, McCauliffe DP, Seykora J, Werth VP. Annular erythema of Sjogren's syndrome in a white woman. *J Am Acad Dermatol*. Jun 2000;42(6):1069-72. [Medline].
32. Hammi AR, Al-Hashimi IH, Nunn ME, Zipp M. Assessment of SS-A and SS-B in parotid saliva of patients with Sjogren's syndrome. *J Oral Pathol Med*. Apr 2005;34(4):198-203. [Medline].
33. Hansen A, Lipsky PE, Dorner T. Immunopathogenesis of primary Sjogren's syndrome: implications for disease management and therapy. *Curr Opin Rheumatol*. Sep 2005;17(5):558-65. [Medline].
34. Hayashi N, Koshiba M, Nishimura K, et al. Prevalence of disease-specific antinuclear antibodies in general population: estimates from annual physical examinations of residents of a small town over a 5-year period. *Mod Rheumatol*. 2008;18(2):153-60. [Medline].
35. Heimbacher C, Hansen A, Pruss A, et al. Immunoglobulin Vkappa light chain gene analysis in patients with Sjogren's syndrome. *Arthritis Rheum*. Mar 2001;44(3):626-37. [Medline].
36. Hulkkonen J, Pertovaara M, Antonen J, Lahdenpohja N, Pasternack A, Hurme M. Genetic association between interleukin-10 promoter region polymorphisms and primary Sjogren's syndrome. *Arthritis Rheum*. Jan 2001;44(1):176-9. [Medline].
37. Iniguez C, Mauri J, Medrano M, et al. [Sjogren's syndrome and multiple sclerosis]. *Neurologia*. May 2001;16(5):232-5. [Medline].
38. Inoue H, Tsubota K, Ono M, et al. Possible involvement of EBV-mediated alpha-fodrin cleavage for organ-specific autoantigen in Sjogren's syndrome. *J Immunol*. May 1 2001;166(9):5801-9. [Medline].
39. Ishimaru N, Saegusa K, Yanagi K, Haneji N, Saito I, Hayashi Y. Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjogren's syndrome through fas-mediated apoptosis. *Am J Pathol*. Jul 1999;155(1):173-81. [Medline].

40. Jadvar H, Bonyadlou S, Iagaru A, Colletti PM. FDG PET-CT demonstration of Sjogren's sialoadenitis. *Clin Nucl Med*. Oct 2005;30(10):698-9. [Medline].
41. Johnson EO, Moutsopoulos HM. Neuroendocrine manifestations in Sjogren's syndrome. Relation to the neurobiology of stress. *Ann N Y Acad Sci*. 2000;917:797-808. [Medline].
42. Karaiskos D, Mavragani CP, Makaroni S, et al. Stress, coping strategies and social support in patients with primary Sjogren's syndrome prior to disease onset: a retrospective case-control study. *Ann Rheum Dis*. Jan 2009;68(1):40-6. [Medline].
43. Kuhn A, Richter-Hintz D, Schuppe HC, Ruzicka T, Lehmann P. [Annular erythema in Sjogren syndrome. A variant of cutaneous lupus erythematosus?]. *Hautarzt*. Apr 2000;51(4):270-5. [Medline].
44. Lester S, Danda D, Cavill D, Pile K, Downie-Doyle S, Rischmueller M. Humoral immunity to Ro52 is not associated with the Ro52 9571 C/T polymorphism in Australian patients with primary Sjogren's syndrome. *Arthritis Rheum*. Nov 2003;48(11):3293-4. [Medline].
45. Leung KC, McMillan AS, Cheung BP, Leung WK. Sjogren's syndrome sufferers have increased oral yeast levels despite regular dental care. *Oral Dis*. Mar 2008;14(2):163-73. [Medline].
46. Maeda M. Dermoscopic patterns of the filiform papillae of the tongue in patients with Sjogren's syndrome. *J Dermatol*. Feb 2006;33(2):96-102. [Medline].
47. Moody M, Zipp M, Al-Hashimi I. Salivary anti-spectrin autoantibodies in Sjogren's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. Mar 2001;91(3):322-7. [Medline].
48. Nakken B, Jonsson R, Bolstad AI. Polymorphisms of the Ro52 gene associated with anti-Ro 52-kd autoantibodies in patients with primary Sjogren's syndrome. *Arthritis Rheum*. Mar 2001;44(3):638-46. [Medline].
49. Ng KP, Isenberg DA. Sjogren's syndrome: diagnosis and therapeutic challenges in the elderly. *Drugs Aging*. 2008;25(1):19-33. [Medline].
50. Okubo H, Maekawa H, Ogawa K, et al. Pseudolymphoma of the liver associated with Sjogren's syndrome. *Scand J Rheumatol*. 2001;30(2):117-9. [Medline].
51. Ostuni P, Botsios C, Sfriso P, De Sandre P, Semerano L, Todesco S. [Diagnosis and classification of primary Sjogren syndrome. Comparison of 3 criteria sets in 219 cases]. *Recenti Prog Med*. Jan 2001;92(1):32-6. [Medline].
52. Ozaki Y, Amakawa R, Ito T, et al. Alteration of peripheral blood dendritic cells in patients with primary Sjogren's syndrome. *Arthritis Rheum*. Feb 2001;44(2):419-31. [Medline].
53. Pertovaara M, Antonen J, Hurme M. Th2 cytokine genotypes are associated with a milder form of primary Sjogren's syndrome. *Ann Rheum Dis*. May 2006;65(5):666-70. [Medline].
54. Pokrzywnicka-Gajek I. Sjogren's syndrome. *Przegl Dermatol*. 2001;88:207-213.
55. S