5-2004

Sjogren's Syndrome: Recognizing and Treating an Autoimmune Disease

Susan M. DeNisco
Sacred Heart University, deniscos@sacredheart.edu

Linda Ferro

Recommended Citation

DeNisco, S. & Ferro, L. (2004). Sjögren's syndrome: Recognizing and treating an autoimmune disease. *American Journal for Nurse Practitioners*, *8*(5), 9–21.

SJÖGREN'S SYNDROME: *Recognizing and Treating an Autoimmune Disease*

Susan DeNisco, APRN, MS, FNP
Linda Ferro, MSN, APRN, FNP

Sjögren's syndrome, one of the most common autoimmune diseases, is characterized by cell-mediated lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal glands.[1] It receives little attention in the literature, and frequently goes unrecognized until progressive changes are apparent. This article aids nurse practitioners in diagnosing the disorder in its earliest stages and in initiating proper treatment.

Sjögren's syndrome was first identified in 1933 by a Swedish ophthalmologist named Henrik Sjögren, who reported the association between dryness of the mouth (xerostomia), dryness of the eyes (xerophthalmia), and chronic deforming arthritis. It can develop as a primary disorder (classic clinical features include parotid gland enlargement, xerostomia, and xerophthalmia), or it may be secondary to an extraglandular connective tissue disease, typically rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis, systemic sclerosis, or biliary cirrhosis.[1-3] Primary Sjögren's is sometimes referred to as keratoconjunctivitis sicca (KCS), the sicca complex, or the sicca syndrome. In either its primary or secondary form, Sjögren's syndrome may progress in severity and lead to end-organ damage.

Incidence

Sjögren's syndrome affects 2 to 4 million persons in the United States, predominantly middle-aged women in the perimenopausal or postmenopausal stage of life (it is 10 times more common in females than in males). The mean age at diagnosis is 50 years.[3] Sjögren's syndrome occurs in persons of all races, but it is rarely seen in children. Thirty percent of patients with autoimmune rheumatic disease suffer from secondary Sjögren's.[1]

Pathophysiology

The pathophysiologic process appears to be autoimmune in nature. Antibodies produce sensitized lymphocytes, which selectively seek, infiltrate, and destroy exocrine glandular tissue. This phenomenon is characterized clinically by depressed production of tears and saliva.[2] Over time, the attack on the body's immune system may lead to inflammation of internal organs, causing irreversible damage. The specific cause of Sjögren's remains unknown, but it is likely that genetic, environmental, and infectious factors are involved.[4] Retroviruses, Epstein-Barr virus (EBV), and, most recently, hepatitis C virus (HCV) have been implicated as causative pathogens.[5] Evidence also suggests that certain hormones, particularly estrogen, may influence the autoimmune response in a manner similar to that noted in diabetes or thyroiditis.[6]

Clinical Presentation

In clinical practice, two presentations of Sjögren's syndrome are seen most frequently. One is the rapid development of severe xerostomia and xerophthalmia, which is frequently accompanied by episodic parotid swelling in an otherwise healthy person (primary Sjögren's). Female patients are also likely to experience vaginal dryness. The other presentation is the insidious and slowly progressive development of the sicca complex

in patients with RA or another connective tissue disorder (secondary Sjögren's).[1,2] Because the symptoms of decreased salivary and lacrimal function are often subtle, the diagnosis is often delayed until severe symptoms are present. Other early manifestations of secondary Sjögren's syndrome may include fatigue, arthralgias, Raynaud's phenomenon (intermittent bilateral ischemia of the fingers, toes, and sometimes the ears and nose, with severe pallor and often paresthesias and pain, usually brought on by cold and relieved by heat), loss of appetite, and weight loss. It is not uncommon for 8 to 10 years to elapse between symptom onset and the development of extraglandular complications.[1]

Diagnosis

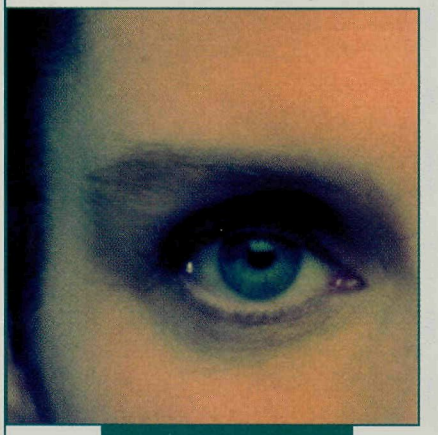
As an autoimmune disease, Sjögren's syndrome can pose a challenge to primary care practitioners in terms of diagnosis, particularly in the early stages. An accurate diagnosis of Sjögren's is obtained through a comprehensive history, a focused physical examination, and selective diagnostic testing. Table 1 lists signs and symptoms that are characteristic of the syndrome. These clinical features should be considered in the review of symptoms when Sjögren's is part of the differential diagnosis.[4] Table 2 lists the San Diego diagnostic criteria for Sjögren's syndrome.[7] These criteria are stringent, requiring evidence for an autoimmune process associated with destruction of salivary and lacrimal gland tissues. At the other extreme, several groups (including the Copenhagen and EEC Study group) have based their diagnostic criteria for Sjögren's syndrome on clinical findings of dry eyes and mouth, with no absolute requirement for gland biopsy or presence of autoantibodies.[7] The EEC study group believes that the San Diego criteria identify only the tip of the iceberg—namely, those patients with full-blown disease—and ignore those patients with milder forms of Sjögren's syndrome.[7]

Differential Diagnosis—Sjögren's syndrome is not the only disease process that can cause lacrimal and salivary gland dysfunction. A comprehensive differential diagnosis must be considered

TABLE 1 SIGNS AND SYMPTOMS OF SJÖGREN'S SYNDROME[4]

ORAL/SALIVARY MANIFESTATIONS
- Dry mouth
- Fissures and ulcers of the tongue, buccal mucosa, and lips
- Petechial lesions on the hard palate
- Lichen planus-like appearance of buccal mucosa
- Cobblestone appearance of tongue
- Inflamed oral mucous membranes
- Parotid gland hardening and/or enlargement
- Dental caries
- Adherence of food to mucosal surfaces
- Dysphagia (especially dry foods)
- Difficulty chewing
- Reduced salivary flow rates
- Changes in or loss of senses of taste and odor
- Frequency chronic candidiasis infections
- Inability to speak continuously

OCULAR MANIFESTATIONS
- Foreign body sensation
- Decreased tear production
- Inability to tear
- Light intolerance
- Filaments of mucus on corneal surface
- Inflammation, erythema
- Eye fatigue
- Corneal ulcerations
- Increased blinking
- Visual changes



SYSTEMIC OR EXTRAGLANDULAR MANIFESTATIONS

Pulmonary
- Shortness of breath
- Scarring or fibrosis
- Lymphoid infiltrates

Gastrointestinal
- Dysphagia
- Abnormal esophageal motility
- Hepatomegaly
- Biliary cirrhosis
- Decreased appetite
- Weight loss

Genitourinary
- Vaginal dryness
- Dyspareunia

Hematologic/Circulatory
- Vasculitis
- Purpura

Lymphoproliferative
- Generalized lymphomas
- Pseudolymphomas
- Macroglobinemia

Renal
- Renal tubular acidosis
- Nephrogenic diabetes insipidus

Integumentary
- Dry skin
- Chronic inflammation of sweat glands
- Skin ulceration, rashes
- Hyperpigmentation

Neurologic
- Polymyositis
- Peripheral neuropathy
- Cranial neuropathy (trigeminal)
- Cerebral vasculitis
- Inability to concentrate
- Fatigue/sleep disorders
- Depression

Musculoskeletal
- Arthralgias
- Nonerosive polyarthritis
- Extra-articular features of rheumatoid arthritis in secondary Sjögren's syndrome
- Myalgias

TABLE 2 SAN DIEGO CRITERIA FOR DIAGNOSIS OF SJÖGREN'S SYNDROME

The diagnosis of *primary Sjögren's syndrome* is made when two of the following three cardinal features are present:[7]

1. Symptoms and objective signs of ocular dryness (Schirmer's test: <8-mm wetting per 5 minutes, and positive rose bengal staining of cornea to demonstrate keratoconjunctivitis sicca)
2. Symptoms and objective signs of dry mouth
   - –Decreased parotid flow rate using Lashley cups or other methods; and
   - –Abnormal findings from biopsy of minor salivary gland (based on average of four evaluable lobules)
3. Serologic evidence of systemic autoimmunity
   - –Elevated rheumatoid factor >1:320; or
   - –Elevated antinuclear antibody >1:320; or
   - –Presence of anti-SS-A(RO) or anti SS-B(LA) antibodies

The diagnosis of *secondary Sjögren's syndrome* is made when characteristic signs and symptoms of Sjögren's syndrome (as described above) are present along with clinical features sufficient to allow for a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyositis, scleroderma, or biliary cirrhosis.

for primary care patients presenting with dry eyes or mouth and parotid gland enlargement. Nurse practitioners (NPs) need to differentiate Sjögren's from other infiltrative processes, autoimmune diseases, and toxic insults (Table 3). Lack of an absolute laboratory marker of Sjögren's necessitates a diagnosis based on a combination of factors: the presence of auto-antibodies, other assessments, and a clinical correlation.[8]

Diagnostic Testing—Selective diagnostic studies are necessary to aid in the accurate diagnosis of Sjögren's syndrome. According to the San Diego criteria, immunologic tests are not diagnostic by themselves, but they are very helpful when interpreted in conjunction with findings from the history and clinical exam. Once immunologic tests are performed during the initial evaluation, they are generally not repeated often. Primary care providers should use the following list of laboratory studies to differentiate Sjögren's from other immune disorders:

Minor salivary gland biopsy remains the gold standard for definitive diagnosis of Sjögren's syndrome. A probable diagnosis of the syndrome can be based on documented decreased salivary function.[9]

Sjögren's antibodies are frequently found in patients with Sjögren's syndrome. In 80% of patients with primary Sjögren's, anti-SSA (formerly SS-A/Ro) and anti-SSB (formerly SS-B/La) antibodies are present. However, these antibodies are not specific to Sjögren's syndrome, as they are found in 20% to 60% of patients with SLE and in 3% to 10% of those with RA.[10]

Rheumatoid factor (RF) is commonly found in patients with RA, but it may also be found in patients with other connective tissues diseases, including Sjögren's syndrome. A positive RF in a patient with Sjögren's syndrome does not necessarily indicate that he or she has RA as well. An elevated RF (>1:320) and the presence of anti-SSA or anti-SSB antibodies provides evidence of systemic autoimmune disease.[1]

Antinuclear antibody (ANA) is measured to aid in diagnosing SLE. An elevated ANA value (>1:320) signals that practitioners should continue their investigation for autoimmune involvement. The ANA titer may be positive in patients with Sjögren's as well; 90% of those with primary Sjögren's have a speckled ANA pattern that is typical for this disorder.[11] However, this test alone cannot be used to make a definitive diagnosis of SLE (or Sjögren's syndrome, for that matter) without other accompanying signs and symptoms.[12] Clinical features and exam findings have a higher degree of importance in assessing disease activity than does an ANA titer alone.[3]

Erythrocyte sedimentation rate (ESR) is helpful in identifying patients who might have a systemic inflammatory disorder or a connective tissue disorders. An elevated ESR is found in approximately 70% of patients with Sjögren's syndrome.[1]

Immunoglobulins or **gamma globulins** are elevated in many patients with Sjögren's syndrome, especially when there is parenchymal involvement. Immunoglobulin (Ig)G, IgA, and IgM antibodies are helpful in monitoring disease activity, particularly in patients treated with high-dose prednisone and cyclophosphamide.

Additional Diagnostic Testing—NPs should perform a urinalysis and measure blood urea nitrogen and creatinine to determine whether patients with suspected or documented Sjögren's syndrome have renal involvement or inflammatory changes. Chest radiograms may help to assess for subtle signs of inflammation such as pneumonitis.

Salivary function tests demonstrate the amount of saliva production, and, indirectly, the extent of mucosal dryness. Methods of evaluating salivary status include sialometry, sialography, sialochemistry, and imaging (ultrasonography, computed tomography, magnetic resonance imaging [MRI]).[3,13] Ultrasonography or MRI of the parotid glands is useful for determining the presence of glandular cysts, enlargement, and chronic inflammation. Secretory sialography, an invasive procedure, is not typically used in primary care management.[2]

Confirmation of destructive lymphocytic infiltration can be obtained by biopsy of the minor salivary glands in the lower lip. Lesions appear as clusters of lymphocytes that replace and destroy the secretory acinar tissue. Presence of this pattern is characteristic of Sjögren's syndrome.

TABLE 3 DIFFERENTIAL DIAGNOSIS

PAROTID GLAND ENLARGEMENT

Bilateral

Viral infections: mumps, mononucleosis, influenza, EBV, Coxsackie A, CMV, HIV, HCV
Sarcoidosis
Amyloidosis
Sjögren's syndrome
Metabolic: DM, hyperlipidemia, chronic pancreatitis, hepatic cirrhosis
Tuberculosis
Acromegaly
Anorexia or bulimia

Unilateral

Salivary gland neoplasm
Bacterial infection
Chronic sialadenitis
Obstruction
Lymphoma

EBV = Epstein-Barr virus; CMV = cytomegalovirus; HIV = human immunodeficiency virus; HCV = hepatitis C virus; DM = diabetes mellitus.

XEROPHTHALMIA (DRY EYE)

Inflammation

Stevens-Johnson syndrome (erythema multiforme)
Pemphigoid
Conjunctivitis
Blepharitis
Sjögren's syndrome

Neurologic

Impaired lacrimal or eyelid function (cranial nerve impairment)
Blepharospasm (uncontrolled blink reflex)

Toxic

Burns
Drugs: decongestants, antihistamines, antihypertensives, acne treatment, muscle relaxants, tranquilizers, oral contraceptives

Other

Trauma
Hypovitaminosis A
Lid scarring
Anesthetic cornea
Epithelial irregularity
Environmental factors (eg, low humidity, cigarette smoke exposure, high wind environments)

XEROSTOMIA (DRY MOUTH)

Viral Infection

Iatrogenic: Irradiation to head and neck

Organic Disease

Autoimmune disease
DM
Hypertension
Dehydration
Sarcoidosis
HIV infection
Sjögren's syndrome
Psychogenic: depression, anorexia, bulimia, anxiety

Toxins

Medication: antihistamines, antihypertensives; alpha and beta blockers; parasympatholytic agents; antidepressants, especially tricyclic antidepressants; muscle relaxants; antispasmodics

Schirmer's test, which uses filter paper to evaluate tear formation by the lacrimal gland, is easy for NPs to perform in practice. A strip of Whatman No. 41 filter paper is placed under the conjunctival sac for 5 minutes, after which the moistened portion of the paper is measured. Wetting of less than 5 mm is a strong indicator of diminished tear secretion (normal tear production is >10 mm). More reliable diagnostic measures include ocular staining with rose bengal dye and biomicroscopy (slit lamp evaluation). Staining of either the conjunctiva or cornea, best seen with the biomicroscope, indicates that small superficial erosions are present—a sign of primary Sjögren's syndrome.

Treatment

Once NPs make the diagnosis of Sjögren's syndrome, they should use a collaborative approach in terms of managing the disease in order to enhance patient comfort and prevent complications. An ophthalmologist and a dentist and/or otorhinolaryngologist should be consulted for management issues specific to the patient's symptomatology. A rheumatologist or immunologist may be consulted in patients with an exacerbation of symptoms or for re-evaluation. Although Sjögren's is a chronic, incurable illness, nearly all patients can lead productive lives with proper management.

At the same time, NPs should consider the economic burden of the recommended treatment plan. Most of the items discussed below are available over the counter (OTC), and are not covered by insurance. According to the Sjögren's Syndrome Foundation, a typical patient may need to spend $625 to $1500 per year on these products.

Symptom Control—The current treatment approach for patients with Sjögren's syndrome is conservative, and is aimed at symptom control. Treatment can be considered in three phases: (1) external moisture replacement or capture (especially important to treat the oral cavity, eyes, nose, skin, and genital tract); (2) stimulation of endogenous secretions, (especially important for the oral cavity); and (3) treatment of systemic manifestations (ie, pulmonary disease, vasculitis, pseudolymphoma).[14]

Xerophthalmia. The cornerstone of treatment for xerophthalmia is regular use of artificial tears, which are used primarily to increase patient comfort. A variety of artificial aqueous or mucous tear preparations, as well as an ocular ointment, can be used to ease the discomfort of ocular dryness (Table 4).[2] Artificial tears contain a moisture component and in some products, a preservative. Preservative-free solutions are

TABLE 4 TREATMENTS FOR XEROPHTHALMIA[2]

PRESERVED ARTIFICIAL TEARS	NON-PRESERVED TEARS
Absorbotears	AquaSite
Duratears Naturale	BioTears
Hypotears	Cellufresh
Liquifilm	HypoTears PF
Murocel	Ocular Ointment
Tears Plus	Lacri-Lube

theoretically more prone to bacterial infection, although many products are packaged in single-dose vials to reduce this risk. Preserved artificial tears may cause burning or irritation, so alternative products must be considered in these cases. Artificial tears can be used as frequently as needed, and they are available OTC. Some products (eg, lubricating ointments) are more viscous and have longer-lasting effects, but they also leave a residue and are less preferred by patients than are the aqueous products.[8] They are generally reserved for nocturnal use because they can cause significant blurring of vision.

The following guidelines may be useful in helping patients to find the appropriate product(s) to meet their needs: If artificial tears are not lasting long enough, use a more viscous tear, try a tear with a different osmolality, use a tear with a different vehicle, or consider referral to an ophthalmologist for punctal occlusion (see below). If tears burn after instillation, choose a tear with a different preservative or use a non-preserved tear. Patients who dwell in low-humidity environments should start using artificial tears as early in the course of their disease as possible.[2]

If artificial tears do not provide adequate lubrication and comfort, ophthalmologic surgery can be considered. Punctal occlusion can provide temporary blockage with collagen plugs or permanent occlusion with cattery or laser treatment.[2] The purpose of the procedure is to block the punctum, or tear duct, which carries tears and debris away from the surface of the eye. Blocking these drainage ducts prevents tears from draining away too quickly and keeps the eyes lubricated.

Last, patients should consider environmental factors that contribute to dry eyes and cause irritation, such as low-humidity environments (eg, highly air-conditioned spaces, non-humidified heated areas, airplanes), cigarette smoke, and windy conditions. Increasing the use of artificial tears before symptom onset will help to alleviate discomfort and to prevent potential corneal abrasion.[2] Use of humidifiers is helpful, as well as wearing wrap-around sunglasses to decrease tear evaporation when outdoors.

Xerostomia. Dry mouth is a major contributing factor to dental caries. It is important to teach patients with Sjögren's syndrome the importance of good oral hygiene and the need to avoid excess sugars. Topical fluorides are warranted to control tooth decay. Patients can apply fluoride daily, and dental hygienists can apply it at regular visits to protect dental enamel. NPs should also make sure that patients use their toothbrush correctly, and that they floss and massage their gums to remove debris between the teeth. Use of toothpastes targeted at preventing periodontal disease (eg, Retardex, Biotene) can also be helpful.[4] Some patients obtain relief by using oral sprays containing mucins and glycoprotein (eg, Mouthkote, Salivart).

Some patients may need to make dietary modifications such as ingesting soft or moist foods only. Others who retain salivary function may find that salivary flow stimulation is helpful: Sugarless gum, hard candy, and mints can alleviate symptoms and increase saliva production. Pilocarpine tablets (5 mg 4 times daily) can act as a pharmacologic stimulant to increase salivary flow for up to 2 hours after ingestion. The most common side effects of pilocarpine are sweating and gastrointestinal intolerance, which are controllable by decreasing the dose. Pilocarpine is contraindicated in patients with a history of uncontrolled asthma, peptic ulcer disease, acute iritis, narrow angle glaucoma, or unstable cardiovascular disease. Response to pilocarpine may take up to 6 weeks.[15] Cevimeline, an oral muscarinic agonist, has been shown to have a longer peak onset of action than does pilocarpine, and it is an effective adjunct to treatment. The recommended dosage is 30 mg orally 3 times daily.

Excess water consumption can remove mucus from the lining of the buccal mucosa and should be avoided; patients should be informed that frequent small sips of water are preferable for symptom control. NPs should also educate patients about avoiding medications (prescription and over-the-counter) that cause dry mouth.

Classic clinical features of primary Sjögren's syndrome include ***parotid gland enlargement, xerostomia,*** *and* ***xerophthalmia.***

Low-grade oral yeast infections are common in patients with Sjögren's syndrome. Topical antifungal troches are useful in treating this problem.[4] To ensure optimal results, patients who wear dentures should remove them while the antifungal medication is dissolving in the mouth. Dentures must be treated to remove candidal organisms from the surface. This can be accomplished by soaking the dentures overnight in a solution of 1/700 dilution of benzalkonium chloride and then cleaning them

carefully with a toothbrush. In severe cases, oral therapy with a systemic antifungal may be necessary.[2]

Dry skin. Frequent use of creams or lotions may be helpful for patients experiencing dry skin. Vaginal dryness is also a problem for women, and can lead to dyspareunia. Many different vaginal lubricants, including topical estrogen, are available to treat this problem.[2]

Systemic Manifestations—Whereas many patients with Sjögren's syndrome require only local moisturizing therapy for xerostomia or KCS, others may need systemic medication for extraglandular involvement. The armamentarium for treating systemic manifestations includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunomodulating drugs (eg, hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide, gold compounds). Primary care providers must do a risk–benefit analysis for each patient before prescribing such agents.

Disease manifestations of arthralgias, myalgias, lymphadenopathy, and fatigue are generally treated with salicylates, NSAIDs, and frequently hydroxychloroquine. In fact, the lattermost agent is one of the most commonly prescribed medications for patients with Sjögren's syndrome.[2] Although corticosteroids have no therapeutic role in the glandular aspects of Sjögren's, they are useful in patients who have life-threatening complications of the disease,[3] including vasculitis, skin lesions, pneumonitis, neuropathy, and nephritis. These patients are usually very ill, and are hospitalized at this point in their illness. Tapering of the steroids must be done with caution; drugs such as hydroxychloroquine, azathioprine, and methotrexate are useful during the tapering process.[2] Many patients with secondary Sjögren's and underlying connective tissue disease are treated with low-dose corticosteroids. Immunomodulating agents are used to induce remission in patients with acute inflammatory processes of rheumatic conditions and internal organ involvement. By controlling the disease process, these agents may reduce the need for corticosteroids and allow for their eventual discontinuation.[10]

Prognosis

As with most chronic progressive illnesses, the rate of progression of Sjögren's syndrome, either primary or secondary, is highly variable. In general, the oral and ophthalmologic manifestations of the syndrome do not progress. Some patients experience only mild xerostomia and xerophthalmia, which they are able to manage with topical agents. Others experience cycles of good health alternating with episodes of serious illness that are manifested by progression of the disease. This progression may include blurred vision, constant eye discomfort, recurrent candidal infection, swollen parotid glands, hoarseness, dysphagia, and difficulty eating. These problems, along with debilitating fatigue and joint pain, contribute to a decreased quality of life. They may interfere with simple activities such as watching television or reading, as well as with patients' ability to work or drive. Furthermore, patient's with primary Sjögren's syndrome are at increased risk for lymphoproliferative disorders, including non-Hodgkin's lymphoma.[16] Patients with splenomegaly, bilateral parotid enlargement, and a history of radiation treatment are at especially high risk. Secondary Sjögren's can progress to damage the vital organs of the body, complicating the illness and the course of treatment.

Patient Education

Like any chronic illness, Sjögren's syndrome can have a profound impact on patients and family members. All may benefit from a close relationship with the primary care provider, as well as a structured support organization. Helping patients to identify their concerns is paramount in their ability to cope with the illness. Integrating relaxation techniques and referral to a mental health professional may be beneficial for select patients. As direct caregivers, NPs play a key role in educating patients with Sjögren's syndrome. As the disease progresses, they are well suited to counsel and coach patients through these transitions and to educate patients to maximize the effectiveness and efficiency of their treatment regimens. By instructing patients about proper oral hygiene to minimize the risk of oral candidiasis and about proper eye care to prevent dryness, NPs can have a profound impact on patient adherence and quality of care.

Research

Much research has been performed on the genetic basis of Sjögren's syndrome and the nature of the immune component. New data are suggestive of viruses (eg, retroviruses, EBV, HCV) playing a role in pathogenesis. Numerous clinical trials are now recruiting patients to increase clinicians' understanding of hormonal underpinnings, diagnostic techniques, pharmacotherapy, and the long-term effects of the disease.

Conclusion

Sjögren's syndrome is one of the most common autoimmune diseases, yet it can go undiagnosed for 8 to 10 years because of the nature of the signs and symptoms. NPs must be able to recognize the clinical features of the syndrome, to recommend appropriate studies to diagnosis it, to begin treatment, and to make appropriate referrals. Easing symptoms and preventing complications are essential to improving long-term outcomes in the population affected by Sjögren's syndrome. Understanding family dynamics and encouraging family involvement are vital components to the care of any patient with a chronic illness. NPs must think globally in order to educate patients, families, collaborating clinicians, and researchers to advance the recognition and treatment of this autoimmune disease.

Susan DeNisco is an assistant clinical professor and coordinator of the Family Nurse Practitioner Program at Sacred Heart University in Fairfield, Connecticut, and she practices at Southwest Community Health Center in Bridgeport, Connecticut. Linda Ferro is a nurse practitioner in the Section of Endocrinology at Norwalk Hospital, Norwalk, Connecticut.

References

1. Moutsopoulos HM. Sjögren's syndrome. In: Braunwald E, Fauci A, Kasper DL, et al, eds. *Harrison's Principles of Medicine.*

15th ed. New York, NY: McGraw Hill; 2001:1947-1949.
2. Fox RI, Michaelson P, Tornwall J. Approaches to the treatment of Sjögren's syndrome. In: Ruddy S, Harris, E, Sledge CB, eds. *Kelly's Textbook of Rheumatology.* 6th ed. Philadelphia, Pa: W.B. Saunders; 2002;2:1027-1037.
3. Moutsopoulos HM. Sjögren's syndrome. In: Schumacher HR, Klippel JH, Koopman WJ, eds. *Primer of the Rheumatic Diseases.* 10th ed. Atlanta, Ga: Arthritis Foundation; 1993:131-135.
4. Vale DL. Recognition and management of Sjögren's syndrome: strategies for the advance practice nurse. In: Tobias NE, Klemt CS, Leslie M, eds. *Nursing Clinics of North America.* Philadelphia, Pa: W.B. Saunders; 2000;35:267-278.
5. Selva-O'Callaghan A, Rodriguez-Pardo D, Sanchez-Sitjes L, et al. Hepatitis C virus infection, Sjögren's syndrome, and non-Hodgkin's lymphoma. *Arthritis Rheum.* 1999;42(11):2849-2490.
6. Nagler RM, Pollack S. Sjögren's syndrome induced by estrogen therapy. *Sem Arthritis Rheum.* 2000;30(3):209-214.
7. Fox RI, Saito I. Criteria for diagnosis of Sjögren's syndrome. *Rheum Dis Clin North Am.* 1994;20(2):391-407.
8. Lash AA. Sjögren's syndrome: pathogenesis, diagnosis, and treatment. *Nurse Pract.* 2001;26(8):50-58.
9. Gravel GW, Pasten RS. Rheumatology and musculoskeletal problems. In: Rakel R, ed. *Textbook of Family Practice.* 6th ed. St Louis, Mo: W.B. Saunders; 2001:982-983.
10. Smeenk RJ. RO/SS-A and LA/SS-B: autoantigens in Sjögren's syndrome? *Clin Rheumatol.* 1995;14(suppl 1):11-16.
11. Manthrope R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features and disease activity. *J Rheumatol.* 1997;24(50):8-11.
12 Carsons S. *The New Sjögren's Syndrome Handbook: An Authoritative Guide for Patients.* New York, NY: Oxford Press; 1998.
13. Soto-Rojas AE, Villa AR, Sifuentes-Orsornio J, et al. Oral manifestations in patients with Sjögren's syndrome. *J Rheumatol.* 1998;25(5):906-910.
14. Carsons SE. A review and update of Sjögren's syndrome: manifestations, diagnosis and treatment. *Am J Manag Care.* 2001;7(14):S433-S443.
15. Nusair S, Rubinow A. The use of oral pilocarpine in xerostomia and Sjögren's syndrome. *Sem Arthritis Rheum.* 1999;28(6):360-367.
16. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM, and the members of the European Concerted Action of Sjögren's Syndrome. Malignant lymphoma in primary Sjögren's syndrome. *Arthritis Rheum.* 1999;42(8):1765-1772.