Clinical Aspect of Sjorgen's Syndrome

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INTRODUCTION

Sjorgen's syndrome (SS) is a chronic rheumatic autoimmune disease characterized by specific symptoms of Sicca keratoconjunctivitis (SKC) and xerostomia (called Sicca complex) due to decreased secretion of the lacrimal and salivary glands, with or without enlargement of the parotid gland.[1-3]

SS is said to be the second most common autoimmune rheumatic disease after Rheumatoid Arthritis (RA), and is even more common than SLE. However, SS is a disease that is very hard to diagnose.[3] The average time between the onset and diagnosis is approximately 8-9 years. As with other autoimmune diseases, it is most commonly found among women, with a ratio of approximately 9:1.[3,4]

Treatment of SS will always involve many experts, such as neurologists, ophthalmologists, pulmonologists, dermatologists, ENT specialists, gynecologists, and of course, rheumatologists.[4,5]

EPIDEMIOLOGY

The incidence of SS is based on the San Diego criteria, which is approximately 0.5%, while based on the Epidemiology committee of the European Community (EEC), 1992, is approximately 3-5% of the adult population.[5]

A study on 837 women ages over 18 years living in Astakes, Aitoloarnania, Greece, in June 1992, using the EEC criteria, found a 0.60% prevalence of SS (5 out of 837).[6] Positive anti SS-B antibody is found in 1 out of 2500 donor samples (women) examined at random. As many as 40-50% of women with positive anti SS-B antibody suffer from primary SS. This produces the estimate that the incidence of SS is approximately 1:1250. Positive anti SS-B antibody is rarely found in secondary SS.[7]

HISTORICAL BACKGROUND

Several patients with complaints of dry mouth, dry eyes, and chronic arthritis have been reported by several physicians in Europe since 1882 to 1925. In 1888, Mikulicz reported a correlation between patients with enlarged parotid and lacrimal glands with cell infiltration found from biopsy. In 1925, Gaugerot reported 3 patients with atrophy of the salivary and mucous glands, accompanied by progressive insufficiency of gland function. Two years later Houwer emphasized the correlation between filamentous keratitis and chronic arthritis.

In 1933, Heurile Sjorgen reported in detail clinical and histological findings of 19 women with SKC and xerostomia, where 13 among them had chronic arthritis.[1-4] In 1953, Morgan and Castleman concluded that Mikulicz's disease and Sjorgen's Syndrome are actually the same disease entity.

PATHOGENESIS

Patients with SS usually complain of dry eyes and mouth. This is caused by friction of the eyelids, particularly the upper eyelids and the ocular surface, or the tongue to the buccal surface. The movement is usually facilitated by tears and saliva. Each of these lubricants contains hydrate cells with mucine, water, proteins, and growth factors. For example if the water volume is inadequate, the viscosity between movements of the eyelids and eye ball increases, and the patient's eye feel uncomfortable.[4,5,8] The eyelids may even stick to the corneal surface and pull off epithelial cells from their layers. Defect in the conjunctival and corneal surface clinically manifest as SKC.

As a result of the defect in epithelial surface, inflammatory response (release of cytokines and inflam-

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matory cell invasion) ensues. In relation with the inadequacy

Diagnostic Criteria

The San Diego criteria for the diagnosis of primary and secondary SS are as follows:[1,3]

I. Primary SS

A. Symptoms and signs of dry eyes
   1. Schimer test: less than 8 mm of the absorbent paper will be wet in 5 minutes.
   2. Rose test: positive Bengal or fluorescent dye on the cornea and conjunctiva demonstrates SKC.

B. Symptoms and signs of dry mouth
   1. A reduction in salivary excretion rate using the Lashley cup or other method.
   2. Abnormal biopsy of the minor salivary gland (focus score of over or the same as 2 out of 4 evaluated lobes).

C. Signs of systemic immune abnormality
   1. An increase in rheumatoid factor of over 1:160
   2. An increase in antinuclear antibody of over 1:160
   3. The presence of anti SS-A and anti SS-B antibodies (La)

II. Secondary SS

- Specific signs and symptoms of SS with signs resembling Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), polyomyocytis, or scleroderma.
- Exclusion: sarcoidosis, pre-existent lymphoma, inherited immunodeficiency disorder, hepatitis, Sicca keratitis due to other causes, gland enlargement, or autoimmune neuropathy.

Primary SS is diagnosed based on: findings of IA1,2; IB1,2; Ic 1, 2, or 3, and no items from point II. A suspected diagnosis of SS may be established if all items are found, before the results of gland biopsy are available.

CLINICAL MANIFESTATION

Ocular Manifestation

SS patients suffer from dry eyes due to a decrease in the aquous component of the tears. This is caused by a destruction of the serous gland and inhibition of neurovascular innervation. We should bear in mind that a reduction in the production of tears may be caused by age (particularly in women), or in patients receiving drugs with anti-cholinergic effects, such as antidepressants, cold medicines, and certain cardiac drugs.[10]

Imbalance between aquous and mucinous secretion causes a reduction of the stability of the tear film, causing the production of debris on the tear film, creating discomfort. The most specific symptom is progressive burning sensation relieved by the use of synthetic tears. Severe dry eyes in SS patients cause filamentous keratitis (the formation of fine filaments on the front surface of the cornea). These filaments cause a foreign body sensation associated with photophobia and blepharospasm.[9,10]

Other ocular SS symptoms include blepharitis (inflammation of the eyelids) associated with abnormal function of the meibom gland. Photosensitivity is rarely found except in severe conditions.

A simple test that can be conducted in order to evaluate SKC is the Schrimer test. The first Schimer test measures tear production for 5 minutes by softly placing a strip paper on the lower conjunctival eyelid. A normal subject should produce at least 6-8 mm within 5 minutes (Figure 1). Afterwards, the second Schrimer test is conducted to measure the maximum output of the minor and major lacrimal grands. A cotton bud is inserted into the nostrils to stimulate the nasolacrimal reflex. A high results in the second Schrimer test indicates a good prognosis and response towards oral pillocarpin or cevimelin treatment to stimulate gland secretion.[1,3,4,6,8]

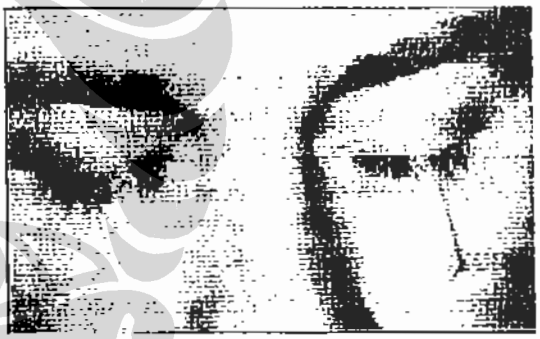

Figure 1

The next is the Bengal Rose test, using a dyed eye drop on the lower conjunctival eyelid, which shows a raccoon image when rinsed with tears with epithelial defect (Figure 2).[11]

Corneal edema and conjunctivitis may also occur, but these are unspecific for SS. Several patients complain of dry eyes at night until they rise in the morning.

Oral Manifestation

Cardinal symptom of SS is xerostomia. This symptom is found in all SS patients. The symptom usually initially occurs during meals, where water is needed to assist swallowing. In women, there is what is called the

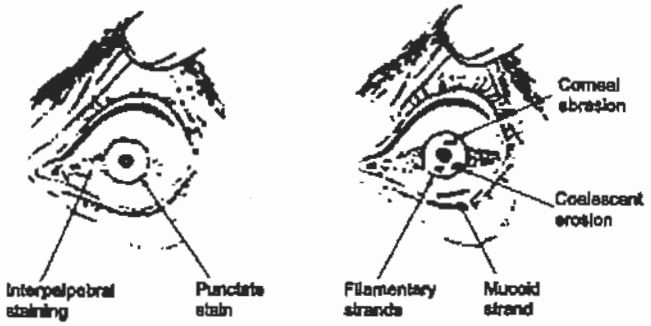

Figure 2. The Bengal Rose Test Shown the Abnormalities from Conjunctivities and Corneal Edema

"lipstick sign", where every time they use lipstick, the lipstick sticks with their front teeth.[12] Patients have a dry tongue and reduced number of papillae. This symptom of dry mouth is unaccompanied by pain, except in case of infection. Salivary dysfunction especially occurs under the tongue, thus facilitating progressive caries due to loss of dental enamel. Caries occur on the gingival front line and incisory surface. Macular erythema may appear, particularly on the dural palate. Chronic erythematous candidiasis of the oral mucosal surface and angular cheilitis are also often found on the edges of the lips.[2,3,8]

Several methods may be used to measure salivary production, such as by placing a cotton sponge under the tongue for 3 minutes and comparing the dry and wet weight. A simpler method is by giving a low sugar candy and measuring the reduction in the size of the candy after 3 minutes.[8] Since there are various conditions that can cause a decrease in salivary production, biopsy of the salivary gland is the choice to diagnose local infiltration of lymphocytes. Biopsy results are evaluated using the Daniels system, where lymphocyte foci are counted (1 focus equivalent to a cluster of 50 or more lymphocytes) per 4 mm. Each pathologist uses a different standard (such as the Chislolm-Mason scale), but the Daniels system is considered the best.[13]

Another method to evaluate and measure salivary function is by using the cyalogram (placing contrast through the Wharton or Stensen ducts). Oil-based contrasts have been abandoned, since they could cause inflammation, in the form of long-standing severe chronic granulomatous reactions that can last for years and develop into parotid infection and lymphoma. In Europe, water-based contrast are more commonly used, but the procedure should be performed by an experienced radiologist.[11,13]

Mass in the neck and salivary glands should be evaluated using magnetic resonance imaging (MRI). Enlargement of salivary glands can occur in diseases such as sarcoidosis, amyloidosis, infection, tumor, HIV, etc.[6,8,9]

Extra-Glandular Manifestations

I. Respiratory Tract

SS is manifested in exocrine glands of the upper respiratory tract in the form of dryness of the nasal and bronchial mucosa. Hunninghake and Fauci found a high incidence of pulmonary abnormality in SS patients, including pleuritis with or without effusion, interstitial fibrosis, interstitial lymphoid disease, chronic bronchitis, or pulmonary hypertension. Respiratory problems are mostly related with mucous plugs.[14] Such condition is aggravated by the use of drugs with anti-cholinergic effects.

Newball and Brahim found proof of mild to moderate respiratory tract obstruction in almost 50% of patients with primary SS.[15] In another study, Oxholm et al found no obstructive changes in 43 patients with primary SS, without noting the pulmonary function capacity. Interstitial pneumonia is estimated to be a rare finding. Seven-year follow up of SS patients did not demonstrate a significant reduction in pulmonary function capacity.[8,9,14]

II. Gastrointestinal Tract

Symptoms involve difficulty swallowing due to lack of production of saliva. Abnormal esophageal motility also contributes to the symptom of dysphagia in patients with primary SS. Increased symptoms of heartburn and discomfort in the distal esophagus is a part of gastric acid reflux in the esophagus, which is not adequately neutralized by saliva due to decreased production. Gastric biopsy demonstrates an increase in the frequency of chronic atrophic gastritis and infiltration of lymphocyte cells. There is also a reduction in the levels of serum pepsinogen and peptin. There may be pancreatic insufficiency with diabetic mellitus and malabsorption. Antipancreatic duct Ag antibody may be found in several patients, but anti-islet cell antibody is not detected.[2,3,9]

III. Skin

The skin becomes dry, particularly due to impaired secretion of sebaceous glands. Oral candidiasis and angular cheilitis are particularly found in SS patients receiving glucocorticoid. Vasculitis in SS patients may take various manifestations. The most common manifestation is hypergammaglobulinemia purpura, which occurs symmetrically on the lower extremities. This is found in patients with an IgG level of over 200 mg/dl.[10,11]

IV. Endocrine

Clinical findings of hypothyroid have been reported in 10-15% of SS patients. Anti-thyroglobuline antibodies and thyroid microsomal antigen may be increased in 4-

5% of patients. The prevalence of Insulin Dependent Diabetes Mellitus (IDDM) and pernicious anemia in primary SS is almost the same as that in the general population.[6,7,10]

V. Kidneys

The most common kidney problem in SS patients is the inability to acidify urine, which is a function of the distal tubules (20-40%). Talal et al demonstrated urine acidification dysfunction in 6 out of 12 SS patients,also characterized by hypergammaglobulinemia. This increases the incidence of nephrocalcinosis.

Proteinuria is rarely found in SS patients. Only 2 out of 36 patients had a urinary protein of over 3.5 g. Glomerulonephritis is also rarely found in SS patients.

VI. Hematology

Leukopenia (a leukocyte count of less than 4000/mm3) is found in 20% of SS patients (6 out of 33). The mechanism of leukopenia is still unclear, but there is a suspicion of the involvement of anti-leukocyte antibodies, spleen sequestration, and abnormal leukocyte maturation in the bone marrow. There are increased levels of cryoglobuline, particularly type II mixed with cryoglobuline containing Ig-M-K monoclonal rheumatoid factor, which resembles that found in Waulden strom's macroglobulinemia. Such increased in the level of cryoglobuline is associated with symptoms of hypergammaglobulinemia purpura.[8,9,11]

VII.Neurology

Manifestations can be central or peripheral in nature. Alexander, et al, found central nervous system disturbance in almost 20% of all patients with primary SS. They found signs of multiple sclerosis by analyzing abnormal cerebrospinal fluid as well as brain MRI. As a comparison, Metz et al, did not find an increase in the frequency of autoantibodies from abnormal labial biopsy among multiple sclerosis patients, but there was an increase in sicca symptoms in patients with systemic sclerosis. Disturbance of the peripheral nerve found in SS patients include peripheral neuropathy and multiplex mononeuritis.[6,8,9,11,12]

MANAGEMENT

The aim of treatment is to reduce symptoms and to prevent advancing disease. Treatment for SS includes topical treatment (eye, mouth, or other body surface), systemic treatment such as that for vascullitis cases, and also non-specific symptoms such as fatigue or sleep disturbance. Sometimes, surgical procedure may be required to deal with certain cases associated with the eyes, mouth, or respiratory tract.[8,12,18]

The usual topical treatment for patients with complaints of dry eyes is synthetic tears. This agent works rapidly and lasts for a short time span. In the last few years, a new formulation with a different electrolyte composition combined with a buffer that is believed to increase penetration into the corneal epithelial cells has been introduced.

Topical treatment for the mouth, such as neutral fluoride, can be used to prevent the formation of caries due to premature enamel loss. In cases of sinusitis in SS patients, a diluted saline solution could be used for sinus drainage. Sometimes, topical nasal corticosteroid, such as budesonide, may be necessary. Artificial tears are classified into those with preservatives and those without. Initially, preservatives such as benzalconium chloride were used in this agent, but this substance cannot dissolve into the patients tear, and could irritate the eyes at high concentrations. In the last decade, a new preservative that causes less irritation was introduced. Synthetic tears without preservatives can now be found in single dose units. Eye drops are usually used at night. If synthetic tears with preservatives cause irritation when used, immediately change to another agent that does not contain preservatives.

The therapeutic approach in SS patients with systemic manifestation is almost the same as in SLE. Even though corticosteroids are effective for SS treatment, it has its shortcoming in long-term use. Some patients respond well with non-steroid anti-inflammatory agents, such as COX-1 or COX-2 inhibitors. For extra-glandular symptoms such as rash or arthralgia, hydrochloroquine (5-7 mg/kg body weight/day) may be administered. In cases with dalciat refractory arthritis, MTX (7.5–15 mg/week) may be administered with folic acid supplementation.[4,5,8,10,11]

A Novel Approach for The Stimulation of Lacrimal and Salivary Functions

As we know, the biopsy results of the minor salivary glands of SS patients demonstrate local lymphocyte infiltration, where the lymphocytes release cytokines such as IL-1 and TNF. These cytokines cause the release of acetylcholine and produce post-receptor signals after neurotransmitter acceptance. In SS patients, it is believed that there is a production of auto-antibodies that can inhibit the response of acetylcholine receptors to begin glandular secretion.[20,21]

Various types of acetylcholine receptors are divided into muscarinic and nicotinic type. The receptor that plays a role in the lacrimal and salivary gland function is the muscarinic N3 receptor. M3 stimulation increases wa-

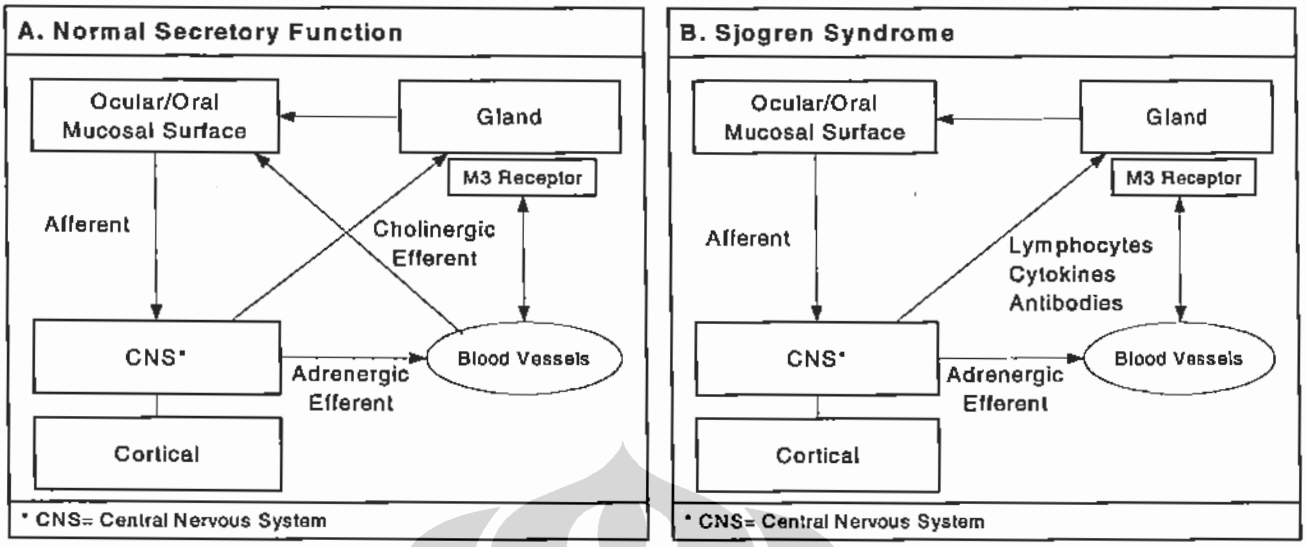

Figure 3. Normal Secretory Function of Lacrimal and Saliva (A) and Patient with Sjogren Syndrome (B)

tery flow from salivary and lacrimal secretion. In 1992, administration of pillocarpin (an acetylcholine analog) can provide comfort for xerostomia patients. This drug can also be used in patients with xerostomia due to radiation treatment around the head and neck. A "double third" (triple blind?–red) controlled trial demonstrated that pillocarpin can be used for the treatment of xerostomia. The dosage used is 4 x 5 mg. A common side effect is increased sweat production and gastrointestinal intolerance, which can be controlled by reducing the dosage.[20,22,23,24]

The most recent drug is cevimeline (also an acetylcholine analog), which demonstrates a higher specificity towards M3 compared to pillocarpin. A study also demonstrates good results for treatment of xerostomia as well as dry eyes. Cevimeline also has a longer half-life compared to pillocarpin (3.7 hour:1 hour) and has a longer occupation compared to M3.[25,26]

CONCLUSIONS

- SS is a chronic autoimmune rheumatic disease that is difficult to diagnose. It is clinically characterized with the presence of sicca complex and specific autoantibodies.
- Clinical manifestations may involve many organs, and thus many experts from various fields also need to be involved in the treatment of the disease.
- Treatment is only aimed at reducing symptoms and preventing disease advancement. Treatment can be topical (for the eyes and mouth) as well as systemic, for SS with systemic manifestations. Even though corticosteroid is effective, it is not the treatment of choice.
- Lacrimal and salivary function may be stimulated using pillocarpin or Cevimeline (the newest drug).

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