Lesson S21: Preanesthetic Assessment of the Patient with Sjögren Syndrome

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
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education for physicians.

Needs statement

Sjögren syndrome received widespread public attention when Venus Williams, one of the most well-known American tennis players, was diagnosed with the disorder and withdrew from the U.S. Open. A survey of anesthesiologists at an academic center indicated that knowledge of this disorder was lacking. The disease, while relatively rare, does occur with some frequency in young people, especially women. Anesthesiologists should be aware of anesthetic consequences of this disorder, especially those related to extreme fatigue, autoimmune disorders and dryness of the mouth and eyes.
Learning Objectives

At the end of this activity, the participant should be able to:

1. State the incidence of Sjögren syndrome
2. Identify the population most likely to be affected
3. Define autoimmune disorder
4. Differentiate between primary and secondary Sjögren syndrome
5. List the symptoms of Sjögren syndrome
6. Describe the Schirmer test
7. Select blood tests that help in diagnosing Sjögren syndrome
8. Choose appropriate preanesthetic tests
9. Create an anesthetic plan for a patient with Sjögren syndrome
10. Anticipate and prevent post anesthetic complications

Case History

A 45 year old female presented for shoulder arthroscopy due to recurrent dislocation. She had been in her usual state of health until about a year or so previously when she noticed increased tiredness. She also noted that her eyes had seemed very irritated for several months and she was required to use artificial tears several times a day. Airway examination revealed many cavities and several loosened teeth. Her BMI was 28.1.

Introduction

Sjögren syndrome is a complex systemic autoimmune disease in which immune cells attack and destroy the exocrine glands that produce tears and saliva.\(^1\)\(^2\) It is primarily a disease of the salivary glands with unknown etiology. Mikulicz disease (MD) was once considered to be a subtype of Sjögren syndrome (SS) but recent studies have suggested that MD is an immunoglobulin G4 related disease and distinguishable from SS by Th2 and regulatory immune reactions that play key roles in IgG4 production.\(^3\)

Sjögren syndrome affects about 4 million people in the United States, making it the second most common autoimmune rheumatic disease. Patients are typically diagnosed after age 40 although the disorder may affect all ages and all races. Women are 9 times more likely to have Sjögren syndrome than men. It is named after Swedish ophthalmologist Henrik Sjögren\(^4\) (1899–1986) who first described the syndrome in 1933.

Sjögren syndrome can occur as a primary disease, or secondary disease following the onset of a rheumatic disorder such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, etc. The autoantigen is alpha-Fodrin.\(^5\)

Autoimmune Disorders

Autoimmune disease occurs when the immune system of an organism fails to recognize its constituent parts resulting in the launch of a harmful immune response against its own cells and tissues. Examples
include coeliac disease, diabetes mellitus type 1, systemic lupus erythematosus, Sjögren syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, and rheumatoid arthritis. Autoimmune diseases are often treated with steroids with varying success.

At the beginning of the twentieth century, Paul Ehrlich, a German biologist and immunologist, proposed the concept of “horror autotoxicus” to describe the body’s innate aversion to immunological self-destruction. Thus, any autoimmune response was perceived to be abnormal and postulated to be connected with human disease. Presently, it is accepted that autoimmune responses are an integral part of vertebrate immune systems (sometimes termed “natural autoimmunity”), normally prevented from causing disease by the phenomenon of immunological tolerance to self-antigens. Autoimmunity should not be confused with alloimmunity, a condition in which the body gains immunity against antigens of another individual of the same species, which are perceived as foreign.

**Signs and symptoms**

The hallmark symptom of Sjögren syndrome is a generalized dryness, typically involving the mouth and the eyes (also referred to as “sicca syndrome”). In addition, Sjögren syndrome may cause skin, nose, and vaginal dryness, and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, peripheral nervous system (distal axonal sensorimotor neuropathy) and brain. (Table 1)

<table>
<thead>
<tr>
<th>Table 1. Effects of Sjögren syndrome on organ systems</th>
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<tbody>
<tr>
<td><strong>Head and neck</strong></td>
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<td>Dry eyes</td>
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<td>Dry mouth</td>
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<td>Dental caries</td>
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<td>Oral sores</td>
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<td><strong>Gastrointestinal</strong></td>
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<td>Difficulty swallowing</td>
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<td>Acid reflux</td>
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<td><strong>Pulmonary</strong></td>
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<td>Pneumonitis</td>
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<td>Interstitial lung disease</td>
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<td><strong>Renal</strong></td>
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<td>Nephritis</td>
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<td>Chronic renal insufficiency</td>
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<td><strong>Hepatobiliary</strong></td>
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<td>Pancreatitis</td>
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<td>Primary biliary cholangitis</td>
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<td>Hepatitis</td>
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<td><strong>Central nervous system</strong></td>
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<td>Decreased concentration</td>
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<td>Depression</td>
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<td>Anxiety</td>
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<td>Extreme fatigue</td>
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<td>Central and peripheral neuropathies</td>
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<td><strong>Hematologic</strong></td>
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<td>Vasculitis</td>
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<td>Anemia</td>
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<td>Raynaud phenomenon</td>
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<td>Lymphoma</td>
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<td><strong>Other</strong></td>
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<td>Thyroiditis</td>
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<td>Arthritis/small and large joint pain</td>
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Sjögren syndrome is associated with increased levels of IL-1RA in cerebrospinal fluid (CSF), an interleukin 1 antagonist. This suggests that increased activity in the interleukin 1 system precedes an auto-regulatory up-regulation of IL-1RA in order to reduce the successful binding of interleukin 1 to its
receptors. It is likely that interleukin 1 is the marker for fatigue, however increases in IL-1RA are observed in the CSF and are associated with increased fatigue through cytokine induced sickness behavior. Patients with secondary Sjögren syndrome may also exhibit signs and symptoms of their primary rheumatic disorders, such as SLE, rheumatoid arthritis or systemic sclerosis.

**Diagnosis**

Although the hallmark symptoms are dry eyes and dry mouth, SS may also cause dysfunction of other organs such as the kidneys, gastrointestinal system, blood vessels, lungs, liver, pancreas, and the central nervous system. Patients may also experience extreme fatigue and joint pain and have a higher risk of developing lymphoma.

Half of all SS patients have “primary Sjögren” and half have “secondary Sjögren”. All instances of SS are systemic, affecting the entire body. Symptoms can remain steady, worsen, or rarely go into remission. While some people experience mild discomfort, others suffer debilitating symptoms that greatly impair their functioning. Early diagnosis and proper treatment are important and may prevent serious complications along with greatly improving a patient’s quality of life. Since symptoms of SS mimic other conditions and diseases, the disease can often be overlooked or misdiagnosed. On average, it takes nearly seven years to reach a diagnosis of SS.

Diagnosis involves detecting the features of dryness of the eyes and mouth. Dryness of the eyes can be determined by testing the eye’s ability to wet a small testing paper strip placed under the eyelid (known as Schirmer’s test). Salivary glands can become larger and harden or become tender. Salivary gland inflammation can be detected by radiologic nuclear medicine salivary scans. Also, the diminished ability of the salivary glands to produce saliva can be measured with salivary flow testing. The diagnosis is strongly supported by abnormal findings of a biopsy of salivary gland tissue.

The glands of the lower lip are often used to obtain a biopsy sample of salivary gland tissue. The biopsy procedure is performed under local anesthesia. A small incision on the inner part of the lower lip is made to expose and remove a sample of the salivary glands within. A biopsy can reveal lymphocytes clustered around salivary glands and damage to these glands due to inflammation. The test carries the risk of damage to the inferior alveolar nerve and of false negatives and a sublingual approach has been suggested as a safer and more reliable alternative.

Diagnosis is often complicated by the wide range of symptoms manifested by the patient, and the similarity between symptoms from SS and those generally associated with other conditions. For example, weakness and fatigue can be associated with many different conditions such as arthritis, multiple sclerosis, or clinical depression. Decreased tear production (keratoconjunctivitis sicca) is common, especially in older women after menopause. Dry eyes are also associated with some medical conditions such as diabetes, rheumatoid arthritis, lupus, scleroderma, thyroid disorders and vitamin A deficiency. Refractive eye surgeries such as laser-assisted in-situ keratomileusis (LASIK) also may cause decreased tear production although symptoms of dry eyes related to these procedures are usually temporary. Damage to the tear glands from inflammation or radiation can hamper tear production. Eyelid problems such as ectropion or entropion also cause dry eyes. Several medications have been implicated including:

- certain types of drugs used to treat high blood pressure, such as central-acting agents and diuretics
• antihistamines and decongestants
• birth control pills
• certain antidepressants
• pain relievers, such as ibuprofen (Advil, Motrin, others) and naproxen (Aleve)
• isotretinoin-type drugs for treatment of acne

Through analysis of the results of a combination of several tests, a correct diagnosis can be made.

Patients with SS typically produce autoantibodies (i.e., antibodies against body tissues) which can be detected through blood testing and include antinuclear antibodies (ANA) that are present in nearly all patients. Rheumatoid factor is often present as SS frequently occurs secondary to rheumatoid arthritis. Typical SS ANA patterns include SSA/Ro and SSB/La, of which SSB/La is far more specific. SSA/Ro is associated with other autoimmune conditions but is often present in SS. 8,9

The Schirmer test measures the production of tears. A strip of filter paper is held inside the lower eyelid for five minutes, and its wetness is then measured with a ruler. Producing less than five millimeters of liquid is usually indicative of SS. However, as previously noted, lacrimal function declines with age or may be impaired from other medical conditions. A slit lamp examination may also detect dryness on the surface of the eyes. An alternative test is nonstimulated whole saliva flow collection, in which the patient spits into a test tube every minute for 15 minutes. A resultant collection of less than 1.5 mL is considered a positive result.10 The test takes longer to perform than a Schirmer test, but does not require specific equipment.

Ultrasound examination of the salivary glands is the simplest confirmatory test and has the added advantage of being non-invasive with no complications. The parenchyma of the gland demonstrates multiple, small (2-6 mm) hypoechoic lesions which are representations of the lymphocytic infiltrates. Often sialectasis with calculi are demonstrated if the disease is advanced. The sonographic findings have excellent symptom correlation. The other advantage of ultrasound is that complications of the disease such as extra-nodal lymphomas can often be detected as larger (1–4 cm) hypoechoic intra-parenchymal masses. Another radiological procedure can be a reliable and accurate means of diagnosing SS. A contrast agent is injected into the parotid duct (of Stensen). Widespread puddling of the injected contrast scattered throughout the gland indicates SS.

The Revised Classification Criteria for Sjögren Syndrome requires the presence of signs, symptoms, and lab findings.11 A recent study emphasized the need for results of a combination of tests. The most common cause of xerostomia was found to be medications rather than SS.12 Patient-reported symptoms must include both ocular symptoms, such as daily, persistent, troublesome dry eyes for more than 3 months, and oral symptoms, such as needing to drink water to swallow food. Objective evidence of eye involvement relies on Schirmer's test and the Rose bengal score (or similar). Histopathology studies should show focal lymphocytic sialadenitis. Objective evidence of salivary gland involvement is tested through ultrasound examinations, the level of unstimulated whole salivary flow, a parotid sialography, or salivary scintigraphy. Autoantibodies against Ro (SSA) and/or La (SSB) antigens are also expected.

Confounding the diagnosis of SS includes past head and neck radiation therapy, hepatitis C infection, acquired immunodeficiency syndrome (AIDS), pre-existing lymphoma, sarcoidosis, graft-versus-host disease, and use of anticholinergic drugs (administered in a time shorter than 4-fold life of the drug).
Low red blood count (anemia) and abnormal blood levels of markers of inflammation (erythrocyte sedimentation rate) are commonly seen and are non specific.

Pathogenesis

While the exact cause of SS is not known, there is growing evidence to support genetic factors and this is an active area of research. The illness is sometimes found in other family members and is more common in families that have members with other autoimmune illnesses, such as systemic lupus erythematosus, autoimmune thyroid disease, type I diabetes, etc. Researchers have used ultradeep sequencing of small RNAs from patients with SS and have identified novel miRNA sequences that may play a role in the disease. Other studies have demonstrated cell mediated autoimmunity that causes apoptosis of the ductal and acinar epithelial cells resulting in glandular tissue damage. A relationship with hormonal activity is suggested by the high ratio (90%) of SS patients that are female.

Treatment

There is neither a known cure for SS nor a specific treatment to permanently restore gland secretion. As such, treatment is generally symptomatic and supportive. The treatment of patients with SS is directed toward the particular areas of the body that are involved and prevention of complications such as infection. There is no cure.

Moisture replacement therapies such as artificial tears may ease the symptoms of dry eyes. Dietary addition of flaxseed oil may also benefit eye dryness. Some patients are advised to use goggles to increase local humidity. For more severe cases of dry eye, punctual plugs are considered. Each eye has two sites at the inner corner of each eyelid where tears drain from the eye. The upper eyelid 'puncta' drains approximately 40% of tears and the lower puncta drains away the remaining 60%. Plugging the lower puncta can result in the tears remaining on the eye longer. Punctal plugs can be inserted into the lower or upper tear drainage canals of the eyes. The procedure takes only a few minutes and is painless. It can be done in the optometrist or ophthalmologist's office. Generally, collagen plugs are inserted first. These plugs will dissolve within a few days, so it gives the patient a chance to see if there is any improvement in comfort. Generally, the improvement is immediate. Permanent plugs may be used, although these too can be removed if necessary. Punctal plugs at < 0.5mm diameter have been shown to improve vital staining scores, break up time and Schirmer test in dry eye related to SS. Additionally, cyclosporin (Restasis®) is available by prescription to help treat chronic dry eye by suppressing the inflammation that disrupts tear secretion.

Dry mouth can be helped by drinking plenty of fluids, humidifying air, and practices to prevent dental decay. The glands can be stimulated to produce saliva by sucking on sugarless lemon drops or glycerin swabs. Additional treatments for the symptom of dry mouth are saliva stimulants, such as pilocarpine (Salagen®) and cevimeline (Evoxac®). These medications should be avoided by people with certain heart diseases, asthma, or glaucoma. Artificial saliva preparations include over-the-counter products, such as toothpaste, gum, and mouthwash (Biotene®). Numoisyn liquid and lozenges are also available for the treatment of dry mouth. Vitamin E oil has been used with some success. Infections of the mouth and teeth should be addressed as early as possible in order to avoid more severe complications. Saltwater (saline) nasal sprays can help dryness in the passages of the nose.
Nonsteroidal anti-inflammatory drugs may be used to treat musculoskeletal symptoms. For individuals with severe complications, corticosteroids or immunosuppressive drugs may be prescribed. Also, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate may be helpful. Hydroxychloroquine (Plaquenil®) has been helpful for some manifestations of SS and is generally considered safer than methotrexate.16 Serious complications, such as vasculitis, can require immunosuppression medications, including cortisone (prednisone and others) and/or azathioprine (Imuran®) or cyclophosphamide (Cytoxan®). Anxiety and depression may require modification with MAO inhibitors or SSRI medications.

Infections, which can complicate SS, are addressed with appropriate antibiotics. Preventive dental treatment is essential as the lack of saliva associated with xerostomia creates an ideal environment for the proliferation of bacteria that cause dental caries (cavities). Treatments include topical fluoride application to strengthen tooth enamel and frequent teeth cleanings. Existing cavities must be filled, as cavities that extend into the tooth cannot be effectively treated through teeth cleaning alone, and are at a high risk of spreading into the pulp of the tooth, leading to the loss of vitality and need for extraction or root canal therapy. This treatment regimen is the same as that used for all xerostomia patients, such as those undergoing head and neck radiation therapy which often damages the salivary glands, as they are more susceptible to radiation than other body tissues. Cancer of the lymph nodes (lymphoma), a rare complication of SS, requires aggressive therapy.

New treatments are likely to be made available in the near future. Recent investigations include multiple monoclonal antibodies17 with the most promising being the anti-CD20 rituximab and the anti-CD22 epratuzumab. Anti-TNF-α and IFN-α drugs have been shown to be less effective. An animal model of SS has been developed by immunizing mice with 60 kD Ro peptide. Days after immunization, salivary flow was decreased and lymphocyte infiltrates, as well as salivary dysfunction, were observed.18,19

**Prognosis and Complications**

Sjögren syndrome can damage vital organs of the body with symptoms that may plateau or worsen, but the disease rarely goes into remission as with other autoimmune diseases. However, with appropriate symptomatic treatment life expectancy is not significantly shortened in most cases. Some people may experience only the mild symptoms of dry eyes and mouth, while others have symptoms of severe disease. Many patients are able to treat problems symptomatically. Others are forced to cope with blurred vision, constant eye discomfort, recurrent mouth infections, swollen parotid glands, hoarseness, and difficulty in swallowing and eating. Debilitating fatigue and joint pain can seriously impair quality of life. Some patients can develop renal involvement (autoimmune tubulointerstitial nephritis) leading to proteinuria, urinary concentrating defect and distal renal tubular acidosis. One case of severe hypokalemia with acute quadripareisis, bulbar weakness and atrial fibrillation has been reported.20

Patients with SS have a higher rate of non-Hodgkin lymphoma compared to both patients with other autoimmune diseases and healthy people.21 About 5% of patients with SS will develop some form of lymphoid malignancy.22 Patients with severe cases are much more likely to develop lymphomas than patients with mild or moderate cases.23 The most common lymphomas are salivary extranodal marginal zone B cell lymphomas (MALT lymphomas in the salivary glands)21 and diffuse large B-cell lymphoma.23 Among the complications discussed above, SS in women who become pregnant has been
linked to increased incidence of neonatal lupus erythematosus with congenital heart block requiring a pacemaker.\textsuperscript{24}

**Preanesthetic management**

In the case presented, the patient reported severe fatigue noting that she sometimes unable to get out of her car when driving to the gym to exercise. She requested a prescription for Restasis\textsuperscript{®} from her doctor to relieve her eye dryness. She also noted that she had joint pains in her fingers and numbness in her feet which she attributed to cold weather and getting older and reported some ankle swelling, especially at night. She was observed taking frequent sips from a bottle of water that she was carrying but did not perceive that as abnormal. The previous month, she had had an upper respiratory infection that was very slow to resolve. Frequent heartburn was being treated with a regimen of Prilosec\textsuperscript{®}. She claimed to see her dentist frequently noting that she had chronic dental problems. One sibling was diagnosed with SLE and her mother had type 1 diabetes.

The patient was referred for an evaluation for Sjögren syndrome. A Schirmer test and salivary production test were performed and both were positive for SS. Other tests included chest X-ray which showed some old scarring and minimal, old, basal atelectasis but no acute disease. Cardiogram was normal. Laboratory blood testing showed a hemoglobin of 10.2 gm. Blood was typed and screened. Both BUN and creatinine were slightly elevated. Thyroid function tests were normal. Liver function tests were also within normal limits. Further testing of antinuclear antibodies revealed high levels of SSA and SSB. Based on all findings, a diagnosis of SS was made. Prior to surgery, the patient was referred for dental examination and several decayed teeth were removed. Anesthetic options were discussed.

**Management of the Case**

The patient requested that she not be paralyzed during the arthroscopic procedure. As no anesthetic technique is preferable, the use of a neuraxial block was considered. No antiallogogues were used. After antacid prophylaxis, she was premedicated with midazolam 1.5mg. A supraclavicular block was performed under ultrasound guidance. During the case, an infusion of propofol 25ug.kg.min was given. She was awake at the conclusion of the surgery and was discharged to home after 6 hours. She was asked to return within the week for further evaluation and therapy of SS. She was also advised to avail herself of support groups which are listed on the web site of the Sjögrens Syndrome Foundation (www.Sjogrens.org).
REFERENCES


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**Post-test**

1. **Which of the following statements is TRUE regarding Sjogren Syndrome (SS)?**
   a. Women are more likely to have it than men.
   b. All races or ethnic groups are susceptible.
   c. SS can be found in all age groups.
   d. All of the above

2. **The approximate number of people with Sjögren syndrome in the United States is:**
   a. 500,000
   b. 4 million
   c. Unknown
   d. Changes each year depending on immigration patterns

3. **Autoimmune disease:**
   a. Is always an inherited trait
   b. Is the same as alloimmunity
   c. Always responds to treatment with steroids
   d. Is an organism’s normal immune response acting against itself

4. **Hallmark symptoms of Sjögren syndrome are least likely to include:**
   a. Generalized urticaria
   b. Xerostomia
   c. Dry eyes
   d. Fatigue

5. **Schirmer’s test detects:**
   a. Salivary gland dysfunction
   b. Decreased tear production
   c. Antinuclear antibodies
   d. All of the above
6. **Dry eye syndrome may be associated with:**
   a. Ibuprofen
   b. Rheumatoid arthritis
   c. Vitamin A deficiency
   d. All of the above

7. **Indicative of Sjögren syndrome is:**
   a. Collection of only 3ml saliva over 15 minutes
   b. Demonstration of hypoechoic lesions in the salivary glands
   c. A negative slit lamp test
   d. Absence of autoantibodies against Ro(SSA)

8. **The treatment of SS symptoms includes:**
   a. Prophylactic antibiotic treatment
   b. Medication to preserve renal function
   c. Punctal plugs
   d. Radiation of the head and neck

9. **Preanesthetic assessment of patients with Sjogren syndrome should include:**
   a. Dental state
   b. Kidney function
   c. CBC
   d. All of the above

10. **In determining anesthetic management:**
    a. General anesthesia is always preferable
    b. All anesthetic options can be explored
    c. Glycopyrrolate is always indicated
    d. The patient should be awake to ensure there is no eye damage