

## **Sjögren's Syndrome, Part I Clinical Manifestations**

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Sjögren's Syndrome is characterized by symptoms of dryness in the mouth, or lack of adequate tear production. This is because the glands that make tears (lacrimal glands) and saliva (parotid glands) become inflamed. Sometimes the inflammation makes these glands painful and swollen, but often, they just cease to function. Sjögren's Syndrome is a condition that is caused by the immune system attacking the tissues of the body. There are several such "autoimmune" diseases, such as Rheumatoid Arthritis and Systemic Lupus Erythematosus ("Lupus"). We call them Connective Tissue Diseases.

### **Incidence**

There are no good figures on the true prevalence of Sjögren's Syndrome, because it is difficult to diagnose and define. For example, many people have dry eyes or dry mouth, but do not have evidence of autoimmune disease. Other people may actually have the disease, but are not diagnosed. In Canada, there are an estimated 327,000 people with Sjögren's Syndrome. About half of these people suffer with the disease as a complication of another autoimmune illness, such as Rheumatoid Arthritis. The remainder have primary Sjögren's Syndrome, wherein there is no other Connective Tissue Disease evident. This condition is seen in women 6 to 7 times more frequently than in men. The peak ages are 30 to 60, but children and the elderly can have Sjogren's Syndrome. All ethnic groups can be affected.

### **Clinical Manifestations**

A person with Sjögren's Syndrome may appear perfectly normal. However, the eyes feel as if they have gravel in them, and the bright sunlight is difficult to tolerate. The eyes may burn, and there is difficulty keeping the eyelids open. Sometimes the eyes become red, crusting can occur around the eyelid margins, and discharge may appear in the corners. Sometimes the eyelids stick together in the morning.

The mouth feels dry, and often, this is misinterpreted as thirst. People carry water bottles around with them. Dry food cannot be swallowed without liquids, and fissuring (cracking) can occur at the angles of the mouth. The teeth begin to decay, often with the development of caries at the gumline. The front teeth can become grinded down and there is fragmentation. The tongue can become sore and sensitive to spices; it can appear red, enlarged and furrowed. Talking can become difficult, as the tongue sticks to the roof of the mouth, and clicks.

Some people develop swelling of the parotid glands, giving the appearance of mumps. This is often on one side at a time, but can eventually become bilateral. The swelling can

be without symptoms, can come and go, and eventually, just persist. This occurs because the glands are inflamed. Some people with Sjögren's Syndrome actually develop episodes of "parotitis". During such attacks, the parotid gland becomes quite painful and swollen; there can be fever. Antibiotics do not always work in this situation, and the pain and swelling usually abate spontaneously over two or three weeks. This can become recurrent, and sometimes the glands can become chronically infected, needing to be removed.

Although Sjögren's Syndrome is primarily a disease in the salivary and lacrimal glands, there can be *systemic manifestations*. Most people with this disease complain of *fatigue*. The fatigue can become quite profound and intrusive. It likely occurs because of the chronic inflammation persisting in the body, but people often overindulge in water intake through the day, then must waken through the night to urinate. Depression can be a factor.

*Joint and muscle pain* can be minor, but there is occasionally severe inflammation. Sjögren's Syndrome can also cause dryness of the nose, skin, sinuses, airways and vagina. It can be associated with *chronic inflammation in the lungs*, and can inflame the *kidneys*, leading to abnormalities of the body's chemistry. Liver disease is seen in about 10% of Sjögren's patients, particularly a rare form known as "*Primary Biliary Cirrhosis*". The blood vessels in the skin can become inflamed ("*vasculitis*"), causing small purple/black spots to occur, usually over the lower legs. The blood vessels in the fingers become very sensitive to the cold, and go into spasm easily, causing white, sometimes purple, numb fingers. This is known as *Raynaud's Phenomenon*. The sensory nerves to the fingers, hands, toes and feet can become impaired, leading to a chronic loss of sensation ("*sensory neuropathy*").

Although most women with this disease are beyond their prime child-bearing years, *pregnancies with Sjögren's* can result in congenital heart block in the newborn. The baby is born with a very slow pulse, and may need a pacemaker. Neonatal lupus, a syndrome of skin rash that usually subsides after 3 months, can be seen in mothers with Sjögren's. The incidence of these complications appears to be less than 6% of births among patients.

*Non-Hodgkins B-Cell Lymphoma* occurs in somewhere between 5 and 10% of patients with Sjögren's Syndrome. Usually, this is a slow growing, low-grade malignancy, that can be cured if discovered. It occurs perhaps with greater frequency in patients who have chronic swelling in the parotid glands. The glands develop a new lump, or lymph nodes in the neck are felt to be swollen. The diagnosis is not easy, and requires a biopsy with special studies on the specimen.

### **Laboratory Manifestations**

There are certain antibodies that are seen more frequently with Sjögren's Syndrome. They are antibodies against particles within the nucleus of normal cells. About 85% of patients have *anti-Ro* antibody and about 50% have *anti-La* antibodies. These sometimes go by another set of names, *anti-SSA* and *anti-SSB* respectively. Patients with Sjögren's Syndrome also quite frequently have *antinuclear antibodies*. This is a screening test for

autoimmune disease, and is quite sensitive, but actually can sometimes be negative, even when anti-Ro or –La are positive. *Rheumatoid factor* is a blood test that is seen with Rheumatoid Arthritis, but this is frequently abnormal in patients with Sjögren’s Syndrome as well. Most of the other blood test abnormalities seen with this condition reflect the fact that the body is in a state of chronic inflammation. These tests include low *haemoglobin*, a low *white blood cell count*, a high *sedimentation rate* and elevated *gamma globulins* (the protein segment of the blood that carries all the antibodies).

### **Making a Diagnosis of Sjögren’s Syndrome**

Sjögren’s Syndrome, like many autoimmune diseases, cannot be diagnosed from one test. Since 2002, European and American Rheumatologists specializing in this disease have agreed upon a set of criteria (**Table 1**). The purpose in creating these criteria was to assure that research was being conducted on a uniform group of patients. Non-the-less, many specialists use the criteria to assure that they have the correct diagnosis. Four of six categories must be found abnormal. One of those categories must either be (VI) a positive *anti-Ro and/or anti-La antibody*, or (IV) an abnormal *minor salivary gland biopsy*.

The biopsy, done using local freezing, is a minor incision on the inside of the lower lip. The glands are the bumps you feel when you run your tongue inside your lip. The pathologist must be familiar with the consensus criteria, because the biopsy must be interpreted in a specified manner. If the biopsy is performed in a centre unfamiliar with Sjögren’s Syndrome, the interpretation will be of no assistance. A biopsy is, furthermore, of limited use unless the patient has at least three other features of the disease, because false positive biopsies are seen in 10-15% of cases.

The other four categories of criteria include (I) *complaints of dry eyes* severe enough to require artificial tears three time daily or more, (II) *dry mouth or swelling* of the parotid gland, (V) *abnormal salivary gland function* (less than 1.5 ml of saliva in 15 minutes, or an abnormal salivary gland scan, or an abnormal dye injection into the gland, known as a sialogram and (III) objective findings of dry eye including *abnormal Schirmer’s Test or Rose Bengal staining* (a red dye). The Schirmer’s Test is a special strip of blotting paper that hangs down from the lower eyelid for 5 minutes. The column of wetness is measured. By criteria, this should be less than 5mm. A diagnosis of “*Secondary Sjögren’s Syndrome*” requires the prior diagnosis of another autoimmune disease, the complaint of either (I) dry eyes or (II) dry mouth, and the objective evidence of two of (III) dry eye, (IV) abnormal minor salivary gland biopsy or (V) abnormal salivary gland.

Adapted from *Annals of the Rheumatic Diseases* 2002;61:554

**Table 1 Revised international classification criteria for Sjögren's syndrome**

**I. Ocular symptoms: a positive response to at least one of the following questions:**

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

**II. Oral symptoms: a positive response to at least one of the following questions:**

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

**III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:**

1. Schirmer's I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
2. Rose bengal score or other ocular dye score ( $\geq 4$  according to van Bijsterveld's scoring system)

**IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per  $4 \text{ mm}^2$  of glandular tissue**

**V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:**

1. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts<sup>19</sup>
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer<sup>20</sup>

**VI. Autoantibodies: presence in the serum of the following autoantibodies:**

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both