



SJOGREN'S SYNDROME
A Study of
THE CORRELATION BETWEEN CLINICAL MANIFESTATIONS
AND SEROLOGICAL FINDINGS

THESIS
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**INTRODUCTION
AND AIM OF THE WORK**

INTRODUCTION AND AIM OF THE WORK

Sjogren's syndrome (SS) is an auto immune disease of the exocrine glands, involving in particular the salivary and lacrimal glands. It may occur alone (primary SS) or in association with a variety of Connective tissue diseases(CTD) and auto-immune disorders (secondary SS). The spectrum of presentation of the disorder is very broad, ranging from the local consequences of exocrine gland dysfunction to major, life threatening systemic complications such as vasculitis, and renal or lung involvement. Furthermore a significant proportion of patients with Sjogren's Syndrome may develop malignant lymphoproliferative disorders such as B cell lymphoma or multiple myeloma (Vitali et al 1993). The primary Sjogren's syndrome is characterized by lymphocytic infiltrate of exocrine glands and extra-glandular structures, polyclonal B_ cell activation and the production of organ and non organ specific auto antibodies. It is A heterogenous disease and diagnostic criteria vary, rendering prevalence studies difficult to compare. Consequently the prevalence of primary Sjogren's syndrome in the community is uncertain although a recent study produce a figure of 2.7 %, making primary Sjogren's syndrome the commonest systemic autoimmune disease. (Foster et al 1992).

One hallmark of SS is the production of auto antibodies. Anti-SSA/Ro, Anti-SSB/La and RF are Found frequently in the sera of patients of SS. Correlationns between these antibodies and glandular manifestations in primary Sjogren's

Syndrome have been described by Atkinson et al 1990 Individual Extra glandular manifestations such as renal manifestations, Raynaud's phenomenon, lung diseases, Arthralgia, thrombo cytopenia and others have been described to be correlated with the positivity of the serological markers of SS (Vitali et al 1989, Foster et al 1992, Swaak et al 1992, St. clair et al 1992, Tsuzaka et al, 1993). Few researches include the titre of serological tests in the correlation.

AIM OF THE WORK

Correlation between clinical manifestations of SS and the important serological findings of the disease.

The clinical manifestation presented by the studied patients , are classified pathologically into glandular, extraglandular and both glandular and extra glandular manifestations and each is correlated to the serological findings not only to the positivity but also to the titre (of anti-SSA/Ro and anti-SSB/La) allowing more fair comparison than each individual manifestation. Also, the Inter-relationship between either clinical manifestations or Serological findings was studied.

REVIEW OF THE LITERATURE

HISTORICAL OVERVIEW AND CRITERIA OF CLASSIFICATION

I- HISTORICAL PERSPECTIVE

The history of Sjogren's syndrome(SS) can be divided into three periods that may be termed clinical (1888-1950), immunologic (1950-1980), and molecular (1980-present). The dates are arbitrary and actually should be overlapping. Each Period is representative of What was happening in medicine generally at the time. Queen Victoria had just finished celebrating her Golden Jubilee, and Arthur Conon Doyle Published his first Sherlock Holmes Story. Two inventions that would revolutionize the way the Common man lived were introduced in 1888. George Eastman put an inexpensive box camera, the Kodak, in the hands of every family. J.B. Dunlop introduced the pneumatic tire, which in time would lead to motorized travel. In London, Jack the Ripper was spreading terror. Winston Churchil was 14 years old. On January 23,1888, Dr. Johann Mikulicz a surgeon reported to the Society for Scientific Medicine at Konigsberg the case of a 42-year-old married farmer from East prussia presenting with painless bilateral swelling of the lacrimal, parotid, and submandibular glands. There was no lymph node enlargement or organomegaly. The patient was unable to raise his eyelids completely. The parotids presented as smooth elastic tumors. A tumor the size of ahen's egg was palpable under each angle of the jaw. A partial removal of the

lacrimal glands was performed , but the tumors recurred rapidly. Complete surgical excision of the lacrimal glands as well as both submaxillary glands was then performed. The patient returned to work but died unexpectedly of peritonitis in July. All Surgical specimens contained numerous small round cells suggestive of lymphoma.(Bjelle 1987).

Henrick Sjogren Was born in 1899 in Stockholm and received his MD degree from the Karolinska Institute in 1927. He was aware of these earlier case reports and in 1933 published a monograph in Which 13 of 19 patients with dryeyes also had arthritis. Sjogren made two major contributions to this disease. He used Rose Bengal to stain the corneal lesions and introduced the term "Keratoconjunctivitis sicca"(KCS) to describe the eye involvement. Both are still in use today. He also performed important pathologic studies and appreciated that this was indeed a generalized systemic disorder. Because of his interest and enthusiasm, SS continues to receive Worldwide attention and is the subject of numerous studies in several fields of medicine.

There remained the question of the relationship between the disease described by Mikulicz and the dry eye, dry mouth, arthritis illness described by several physicians and put together in the syndrome called Sjogren's Syndrome(SS)(Talal 1992).

II- CRITERIA OF CLASSIFICATION

In fact, several sets of criteria have been proposed and used by different authors but uptill now no international diagnostic criteria have been validated. The following are examples

A- Fox CRITERIA

Robert I Fox recommended the following criteria for diagnosis of primary and secondary Sjogren's Syndrome .

1 - Primary SS.

a - Symptoms and objective signs of ocular dryness.

Schirmer test less than 8 mm Wetting per 5 minutes, Positive Rose Bengal or fluorescein staining of cornea and conjunctiva to demonstrate Keratoconjunctivitis sicca.

b- Symptoms and objective signs of dry mouth

Decreased parotid flow rate using Lashley cups or other methods. Abnormal biopsy of minor salivary gland (focus score of ≥ 2 based on average of 4 evaluable lobules).

c- Evidence of a systemic autoimmune disorder

Elevated rheumatoid factor $\geq 1:320$

Elevated antinuclear antibody \geq 1:320

Presence of anti-SS-A(RO) or anti-SS-B(La) antibodies.

2 - Secondary SS

Characteristic signs and symptoms of SS (described above) plus clinical features sufficient to allow a diagnosis of RA, SLE, polymyositis or scleroderma.

2- Exclusions:

Sarcoidosis, pre-existent lymphoma, acquired immunodeficiency disease and other Known Causes of Keratitis sicca or salivary gland enlargement. (Fox . . 1986).

The frequency of SS in Japan is 29.5 Women and 1.5 men out of the population of 100,000. Its sexual ratio is 38.8 to 1, with women being the overwhelming majority, whose mean age of pathologic development is in their forties.

B-CRITERIA IN JAPAN

The specific criteria conventionally Used in Japan is the one established by the Ministry of Health and Welfare, Japan (Homma et al 1986).

1 - Definite Case

Presence of sicca complex symptoms of unknown cause, together with one or more of the following three features:

- (a) Evidence of idiopathic KCS:(++) or over response in the Rose Bengal a positive fluorescein staining.
- (b) Characteristic pathologic findings Within lacrimal and/or salivary glands: infiltration of more than 50 mononuclear cells around intralobular ducts, found in at least one spot Within a single lobule.
- (c) Definite pathologic findings on sialography: findings of diffuse punctate shadows With diameters of more than 1 mm

2 - Probable Case

Presence of sicca complex symptoms of unknown cause, together with one or more of the following three features :

- (a) Suspicion of idiopathic KCS:(+) response in the Rose Bengal staining, and the wetting of less than 10mm in the Shirmer test, or a positive fluorescein staining.

- (b) Evidence of reduced salivary secretion : less than 10 ml of saliva, after 10 minute gum test.
- (c) Swollen salivary glands of unknown cause, progressing recurrently or chronically.

This criteria is modified from Shearn's criteria. Instead of sialography, however, some doctors have come to prefer sialoscintigraphy. because of its minimal invasiveness. Lip biopsy in Japanese SS Patients is also equivalent to those in the Western Countries, and the same pathologic criteria established by Daniels et al are being used.

Although the basic concepts for the diagnosis and treatment are essentially the same with the western standards, there are several minor modifications Present. (Sugai et al 1987).

C - Recent Preliminary criteria for the classification of Sjogren's syndrome.

1 - Ocular Symptoms

Definition: A Positive response to at least of the following 3 questions"

- (a) Have you had daily, Persistent, troublesome dry eyes for more than 3 months?