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ORIGINAL RESEARCH

Correlation of Tarplay's grading system and diagnosis of patients suspected of having Sjögren's syndrome, achieved at the Centro Médico Nacional «La Raza», México («La Raza» National Medical Center, Mexico)

Correlación de la escala de Tarplay y el diagnóstico de pacientes con sospecha de tener síndrome de Sjögren del Centro Médico Nacional «La Raza»

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ABSTRACT

Aim: To establish any existing correlation between Tarplay's grading system and patients with positive diagnosis of Sjögren's syndrome. **Methods:** 321 cases of patients suspected to be afflicted with Sjögren's syndrome were reviewed at the Highly Specialized Medical Units (UMAE), Centro Médico Nacional «La Raza» («La Raza» National Medical Center). These patients had been referred to the said center between January 2001 and December 2005. Patients had been referred as part of their study protocol. Patients were subjected to labial salivary gland biopsy. The procedure was undertaken under local anesthesia and using the technique described by Daniels. Evaluation was achieved using light microscopy and patients were graded according to Tarplay's grading system. Sjögren's syndrome diagnosis was established based on criteria proposed in 2002 by the Group of American and European Consensus. The main objective criterion used was histopathology of labial salivary glands. **Results:** Direct association was found between Tarplay's index increase of labial salivary gland biopsies and Sjögren's syndrome positive diagnosis. Fisher exact test was used with $p < 0.001$. OR = 0.13, with 95% confidence interval (CI) and 0.004-0.045 rank. No association was found between the degree of fibrosis and positive diagnosis of Sjögren's syndrome. Presence of rheumatoid arthritis and systemic lupus erythematosus was directly associated with secondary positive Sjögren's syndrome ($p < 0.001$, OR = 3.25 with CI 95% = 1.8-5.6 and $p = 0.004$, OR = 4.0 with CI 95% = 1.4-10.9 respectively). **Conclusions:** Histological evaluation of labial salivary glands using Tarplay's grading system is a reliable test to establish diagnosis of Sjögren's syndrome.

RESUMEN

Objetivo: Establecer la correlación que existe entre la escala de Tarplay y los pacientes con síndrome de Sjögren positivo. **Métodos:** Se revisaron 321 casos de pacientes con sospecha de tener síndrome de Sjögren de la UMAE, Centro Médico Nacional «La Raza», los cuales fueron remitidos entre enero del 2001 y diciembre del 2005 al Servicio de Cirugía Maxilofacial como parte de su protocolo de estudio, en donde se les realizó una biopsia de glándulas salivales labiales bajo anestesia local y mediante la técnica descrita por Daniels, siendo evaluadas mediante microscopia de luz y clasificadas con base en la escala de Tarplay. El diagnóstico de síndrome de Sjögren se estableció con base en los criterios propuestos por el Grupo de Consenso Americano y Europeo en el 2002, empleando como principal criterio objetivo la histopatología de las glándulas salivales labiales. **Resultados:** Se encontró una asociación directa entre el incremento del índice de Tarplay de las biopsias de glándulas salivales labiales y el diagnóstico positivo para el síndrome de Sjögren, empleando la prueba exacta de Fisher con una $p < 0.001$, razón de momios (OR) = 0.13 con un intervalo de confianza del 95% y un rango de 0.004-0.045. No se encontró asociación entre el grado de fibrosis y el diagnóstico de síndrome de Sjögren positivo. La presencia de artritis reumatoide y lupus eritematoso sistémico se asoció directamente con el diagnóstico de síndrome de Sjögren secundario positivo ($p < 0.001$, OR = 3.25 con IC 95% = 1.8-5.6 y $p = 0.004$, OR = 4.0 con IC 95% = 1.4-10.9 respectivamente). **Conclusiones:** La evaluación histológica de las glándulas salivales labiales mediante la escala de Tarplay es una prueba confiable para establecer el diagnóstico del síndrome de Sjögren.

Key words: Sjögren's syndrome, salivary glands, Tarplay.
Palabras clave: Síndrome de Sjögren, glándulas salivales, Tarplay.

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INTRODUCTION

Sjögren's syndrome (SS) is a chronic, autoimmune disease characterized by mucosa dryness, which mainly affects oral mucosa (xerostomia) and ocular mucosa (xerophthalmia). It is due to decrease or absence of glandular secretions.[1] Glandular hyposecretion is the result of mechanisms that can be cellular interaction (lymphoplasmacytic infiltrate) or humoral interaction (auto-antibodies and soluble inflammatory mediators) which produce acinar and ductal epithelial cells destruction, with parenchyma loss. Therefore in one patient, all exocrine glands could be affected.[2] Its etiology is as yet unknown. Several causes have been suggested: genetic, hormonal, infectious and immunological, as well as intrinsic and extrinsic factors.[3] SS is the second most frequent autoimmune disease, second only to rheumatoid arthritis. It is believed to affect approximately 0.5-4.8% of the general adult population over 55 years of age.[4-6] Clinical manifestations usually appear between the 4th and 7th decade of life. Average age is 50 to 60 years in post-menopausal females; nevertheless they can appear at any age, from childhood to old age. It appears predominantly in females with a 9:1 relation with respect to males.[2,7]

SS can appear by itself (primary) or associated to other connective tissue disease (secondary).[8] Presently, diagnosis is based upon the classification criteria proposed by the American and European Consensus published in 2002[8] *(Tables I and II)*. The aforementioned are six criteria, they include subjective criteria such as oral and ocular symptoms, and objective criteria such as ocular symptoms, minor salivary glands histopathology, and auto-antibodies. Focal sialadenitis and antibodies are considered the most specific markers for this disease.[8] Nevertheless, it is known that at least 15% of SS patients can escape auto-antibody detection when routinely used methods are employed.[9-11] In histological assessment of salivary glands, lymphocytic infiltrate foci recordings is the most useful histological index to determine seriousness of the disease.[12] Diagnostic profitability of this procedure greatly depends on the suitable harvesting and analysis of the sample.[3,13] Biopsy of labial salivary glands is the most frequently used test as well as the main objective criterion in order to establish diagnosis in patients suspected to be afflicted with SS. Nevertheless, biopsy results are applied to the oral component and not to the full syndrome. Sialadenitis is considered the most specific histological characteristic of SS, since it

Table I. *International classification criteria for Sjögren's syndrome.[8]

I. Ocular symptoms: one positive response to at least one of the following questions:
   1. Have you consistently suffered from dryness in your eyes for over 3 months?
   2. Have you a recurrent feeling of gravel in your eyes?
   3. Do you use artificial tears more than three times a day?

II. Oral symptoms: one positive response to at least one of the following questions:
   1. Have you experienced daily dryness of the mouth for over 3 months?
   2. Have you experienced recurrent increase in the volume of your salivary glands?
   3. Are you frequently drinking liquids in order to achieve oral lubrication?

III. Ocular signs: objective evidence of ocular involvement defined as a positive result in at least one of the two following tests:
   1. Schirmer test performed without anesthesia (- 5 mm in 5 minutes)
   2. Punctuation in the Bengal pink test or other ocular staining (+ 4 according to the van Bijsterverld system)
   3. Salivary scintigraphy exhibiting excretion delay anad/or reduced salivary concentration

IV. Histopathology: in minor salivary glands (harvested from normal looking mucosa) focal lymphocytic sialadenitis, assessed by an expert pathologist with score of + one focus, defining scoring by foci as the number of lymphocytes (which are adjacent to normal looking mucous acini and containing + than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence defined by a positive result in at least one of the following diagnostic tests:
   1. Salivary flow without stimulation (- 1.5 mL in 15 minutes)
   2. Parotid sialography showing presence of diffuse sialectasies without any evidence of obstruction in the major ducts
   3. Salivary scintigraphy to show delays in excretion and/or reduced concentration of saliva

VI. Auto-antibodies:
   1. Antibodies to Ro (SSA), La (SSB) or both

* Taken from Vitali C, Bombardieri S, Moutsopoulos HM et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002; 61: 554-558.[8]

Table II. **Rules for Sjögren's syndrome classification.[8]

Primary SS: in patients without any associated disease can be defined as follows
a. Presence of 4 out of the 6 points indicates primary SS, if point IV or VI are positive
b. Presence of 3 out of the 4 objective criteria (points III, IV, V, VI)
c. Three classification procedure represents a valid classification alternative
Secondary SS: in patients with an associated connective tissue disease, presence of point I or II or any two of points III, IV and V
Exclusion criteria:
Head and neck radiotherapy
Hepatitis C virus infection
Acquired immunodeficiency syndrome
Persistent lymphoma
Sarcoidosis
Graft-host disease
Use of anticholinergic drugs

** Taken from Vitali C, Bombardieri S, Moutsopoulos HM et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002; 61: 554-558.[8]

Table III. *Tarplay's grading scale.[14]

1+ = 1 or 2 mononuclear cellular aggregate per lobule
2+ = 3 or more aggregates per lobule
3+ = diffuse mononuclear cellular infiltration more than focal aggregates, with acinar destruction
4+ = diffuse mononuclear cellular infiltration with complete destruction of lobular architecture
In Tarplay's scale, fibrosis degree is subjectively established in the following manner:
Absent = 0
Minimum = 1+
Moderate = 2+
Severe = 3+

* Taken from Tarplay TM, Anderson LG, White CL. Minor salivary gland involvement in Sjögren's syndrome. Oral Surg. 1974; 37: 64-74.

is possible to also find fibrosis, atrophy and fat infiltration in patients over 50 years of age, who are not exhibiting the syndrome.[3,14,15]

At the «La Raza» National Medical Center, the Rheumatology Service refers to the out-patient Maxillofacial Surgery service all those patients suspected of suffering primary or secondary Sjögren's syndrome. This is part of the study protocol, which includes labial salivary gland biopsy, which is then assessed with light microscopy by the pathological anatomy department and is then classified based on Tarplay's scale *(Table III)*. It is therefore important to determine the correlation existing between Tarplay's biopsies index and the number of positive cases of primary or secondary Sjögren's syndrome.

PATIENTS AND METHODS

A retrospective study was undertaken with 321 cases of patients suspected of being afflicted with SS. Patients were of both genders, and over 18 years of age. Patients were referred from the Rheumatology Service to the outpatient service of the Maxillofacial Surgery Service of the Highly Specialized Medical Units (UMAE), Medical Center «La Raza» Hospital, Mexico City, between January 2001 and December 2005. Patients underwent a biopsy of labial salivary glands. The biopsy was performed under local anesthesia and following the technique described by Daniels.[16] This technique consists of everting the upper lip and performing a 1.5 to 2 cm incision on the labial mucosa, between the midline and the corner, penetrating into the epithelium and releasing the glands from the surrounding fascia. A direct dissection is undertaken, glands are separately removed and placed in 10% formalin. The procedure is then completed with the suture of the incision.

Harvested glands were sent to the hospital's Pathological Anatomy Service, to be routinely processed and dyed with hematoxylin and eosin. The glands were then assessed by expert

pathologists and classified according to Tarplay's scale. Tarplay's[14] scale evaluates presence or absence of diffuse, focal and chronic inflammatory infiltrate (sialadenitis). This scale shows proper balance between sensitivity and specificity (82.4 and 86.2% respectively). It consists on determining the number of aggregates of mononuclear cells (mainly lymphocytes, plasma cells and histiocytes) that can be observed in a 4 mm^2 of glandular tissue, using indexes from 1+ to 4+, where 0 would represent a normal minor salivary gland and considering the fact that each «aggregate» or «focus» is equivalent to 50 cel/4 mm^2. Fibrosis degree was subjectively established as follows: absent = 0, minimum = 1+, moderate = 2+, severe = 3+.

Histopathological results of biopsies were collected and clinical files of patients were assessed so as to determine which cases met with the SS diagnosis criteria proposed by the European and American Consensus Group in 2002.[8] Thus, primary diagnosis of Sjögren's syndrome was established based on positive ocular and oral symptoms, with the help of Schirmer's test. Biopsy of minor salivary glands was used as main diagnosis objective criterion. These glands were to have more than 1 focus of 50 lymphocytes per 4 mm^2 of glandular tissue as per established in Tarplay's scale. Diagnosis of secondary Sjögren's syndrome was established in those cases which exhibited an associated connective tissue condition, as well as presence of oral and ocular symptoms or Schirmer test and biopsy of positive minor salivary glands. Patients exhibiting benign or malign minor salivary gland neoplasia were excluded. Likewise, cases lacking full information in the clinical record or histopathological report were equally excluded. Exclusion also encompassed those cases which exhibited hepatitis C virus infection, acquired immunodeficiency syndrome, pre-existent lymphoma, sarcoidosis, graft-host conflict, or patients using anti-cholinergic drugs.

Ethical considerations

The present study was based on the professional ethics principle which contends that the rights of the individuals overrule society rights, or scientific rights when dealing with future patients. This was established in the Helsinki Statement in 1975, the General Health Law concerning health research, which was amended in 1989 as well as the norms for scientific research of the IMSS (Mexican Institute of Social Security).

Statistical analysis

Correlation between Tarplay´s index of labial salivary gland biopsies and patients with positive Sjörgren syndrome was established by means of Fisher´s exact test. χ^2 test was used to determine the association between secondary SS syndrome patients and related systemic diseases. Disease estimated risk was calculated with an Odds Ratio. All data analysis was conducted with SPSS software, version 15.0.

RESULTS

321 cases were studied, out of which 172 were positive to Sjögren's syndrome, 71 (41%) for the primary type and 101 (59%) for the secondary type. Diagnosis was established based on criteria proposed by the European and American Consensus published in 2002.[8] Gender distribution of positive cases revealed presence of 160 (93%) females and 12 (7%) males. Patients' ages ranged from 18 to 79 years, average was 48.6 years. Signs and symptoms found in positive Sjörgren's syndrome patients were: xerostomia and xerophthalmia in 100% of cases, arthralgia in 23 cases (13.3%), parotid hypertrophy in 11 cases (6.3%), glossodynia in 10 cases (5.8%), xeromicteria in 5 cases (2.9%), sub-mandibular hypertrophia in 4 cases (2.3%) xerodermia, dyspareunia, and lingual papillae atrophy in 3 cases (1.7%) respectively *(Figure 1)*.

In patients afflicted with secondary Sjögren's syndrome the most frequently found systemic condition was rheumatoid arthritis; it was present in 62 cases (61%), followed by systemic lupus erythematosus present in 21 cases (20.3%), sclerodermia in 9 cases (8.9%), osteoarthritis in 5 cases (4.8%), cryoglobulinemia in 2 cases (1.9%), Reiter's syndrome and Raynaud's phenomenon in 1 case (0.5%) respectively *(Figure 2)*. A direct relationship was found between the presence of rheumatoid arthritis and diagnosis of positive secondary SS diagnosis. This relationship was established with the χ^2 test, where $p < 0.001$ was obtained, OR equal to 3.25 with confidence interval of 95% and rank of 1.8 to 5.6. Therefore, for those patients who are suspected to be afflicted with SS and exhibit rheumatoid arthritis, the risk of presenting the disease is trebled. Moreover, an association was equally found between systemic lupus erythematosus and positive secondary SS diagnosis when using χ^2 test; where $p = 0.004$ was obtained OR 4.0 and confidence interval of 95%, rank 1.4 to 10.9. It was observed that patients suspected of suffering from SS and who were afflicted with systemic lupus erythematosus, presented four times over the risk of the illness.

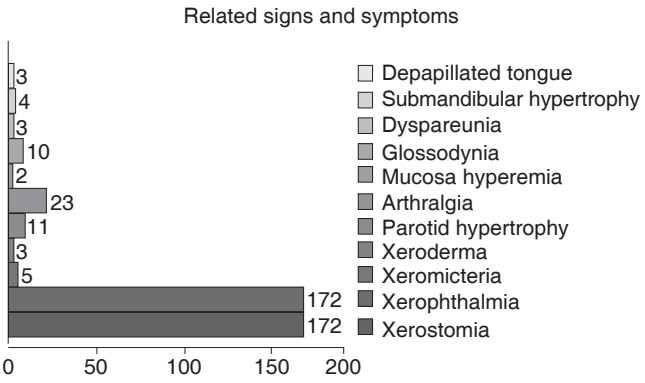

Figure 1. Representation of main signs and symptoms exhibited by patients with positive Sjögren's syndrome.

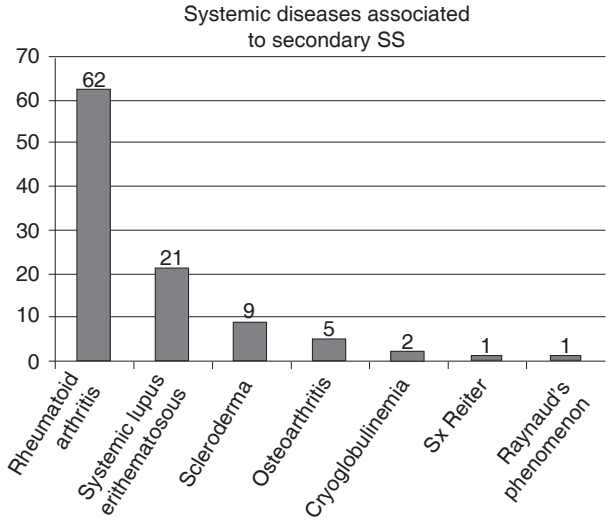

Figure 2. Patients with positive secondary Sjögren's syndrome and associated systemic diseases.

Histopathological results of biopsies of all 321 patients assessed *(Table IV)* revealed the following: none of the 172 cases positive to SS presented a 0 Tarplay index, 40 cases exhibited Tarplay 1+, 64 cases showed Tarplay 2+, 59 cases had Tarplay 3+ and 9 cases Tarplat 4+. Out of the 149 cases which exhibited negative SS, 78 showed Tarplay 0, 68 Tarplay 1+, 2 cases showed Tarplay 2+, 1 case showed Tarplay 3+, and not a single case exhibited a Tarplay 4+ rating. In order to establish association between Tarplay's index obtained in the biopsies and SS positive diagnoses, contingency tables were established. In those tables variables with values lesser than 5 were excluded, therefore, Tarplay's degrees collapsed, and only those cases which exhibited Tarplay 1+, 2+ or 3+ were compared. Fisher's exact test was used, and a direct relationship was found between increase of Tarplay's index of labial salivary glands biopsies and positive SS diagnosis, with $p < 0.001$, OR 0.13, confidence interval of 95% with 0.004 to 0.045 rank. Therefore it can be supposed that to greater Tarplay's index values greater will be the possibility of suffering the syndrome. Out of the 172 cases positive to Sjögren's syndrome, only 89 presented some degree of fibrosis, 56 cases exhibited minimum fibrosis (1+), 23 cases presented moderate fibrosis (2+) and one case showed severe fibrosis (3+). No association was found between biopsies´ degree of fibrosis and SS positive diagnosis.

DISCUSSION

Usage of more specific criteria to establish SS diagnosis is extremely important since an inappropriate diagnosis forces the patient to live with the spectrum of an incurable and potentially progressive illness and at the same time, deprives him of the treatment needed for a reversible condition

Table IV. Histological characteristics of labial salivary glands of all 321 patients suspected of suffering from Sjögren's syndrome.

	Patients with Sjögren's syndrome		
	Positive	Negative	Total cases
Tarplay 0	0	78	78
Tarplay 1+	40	68	108
Tarplay 2+	64	2	66
Tarplay 3+	59	1	60
Tarplay 4+	9	0	9
Fibrosis 0	129	83	212
Fibrosis 1+	56	18	74
Fibrosis 2+	23	1	24
Fibrosis 3+	10	1	11

which imitates Sjögren's syndrome such as secretory hypofunction caused by drugs' collateral effects, meibomitis, blepharitis, allergic conjunctivitis etc. In the present study, SS diagnosis was based on criteria proposed by the American and European Consensus Group in 2002,[8] which include new rules for the correct application of patients with primary and secondary Sjögren's syndrome, as well as an exclusion list. This is a valuable tool for patient diagnosis, using as main objective criterion the histopathology of labial salivary glands. No routine auto-antibody tests were performed at the National Medical Center «La Raza» as part of study protocols of patients suspected of suffering SS, since it is known that at least 15% of SS patients can escape auto-antibody detection performed with routine methods.[10,11] Therefore, labial salivary gland biopsy is considered the main objective criterion to establish an SS diagnosis. Dr Drossos et al in their study of a geriatric male and female population in Greece, found a primary Sjögren's syndrome prevalence of 4.83% based on the presence of keratoconjunctivitis, abnormal proportion of parotid flow as well as recording of more than 2+ foci in labial salivary glands (graded according to Tarplay's scale) 6% of that population exhibited a positive result to ANA (anti-nuclear-antibodies), but none presented Ro or La antibodies.[9] This concurs with findings reported by Vitali[10] and Anaya[11] in their study on the accuracy of auto-antibodies tests.

In 1966, labial salivary gland biopsies were for the first time linked as an important factor of SS diagnosis. Therefore, several tests have been proposed to conduct histological evaluation of labial salivary glands. Nevertheless, most of these studies concur in stating that presence of more than one lymphocyte focus per 4 mm^2 of labial salivary gland tissue is a constant finding in SS patients; this also provides a semi-quantitative measure of the disease's oral component.[15] For Drs Daniels and Whitcher, histological finding of only one focus might represent an early or mild form of the oral component of SS and must raise the suspicion of presence of the disease, nevertheless, this must not be employed as a diagnosis criterion.[6] In our study, we found that out of the 172 cases which were positive to SS, 40 cases presented Tarplay 1+, 64 cases Tarplay 2+, 59 cases Tarplay 3+, and 9 cases Tarplay 4+. This is in agreement with descriptions of Drs Talal,[3] Moutsopolous[16] and Chrisholm[17] who depicted lymphocytic infiltration degree of 2+ to 4+ as typical histological image of Sjögren's syndrome.

In some studies[18-22] it is considered that Tarplay's scale is qualitative and therefore does not adequately differentiate among patterns of salivary gland tissue inflammation. In our study, we found a direct association between increase of Tarplay's index obtained in analyzed labial salivary gland biopsies with a positive SS diagnosis. No relationship was found with the degree of fibrosis, since out of the 172 positive cases, only 89 presented some degree of fibrosis, and out of the 149 negative cases, 20 exhibited fibrosis. This also concurs with findings of Talal,[3] Moutsopoulus[16] and Chrishom[17] who consider that sialadenitis is the most specific characteristic of Sjögren's syndrome, since it is possible to find fibrosis, atrophy and fatty infiltration in subjects over 50 years of age, without any presence of Sjögren's syndrome.

We would like to mention that we found no significant difference with previously reported findings with respect to age of patient at disease onset, its clinical manifestations and predilection for female gender.

CONCLUSIONS

Sjögren's syndrome diagnosis is currently based upon criteria proposed by the American and European Consensus Group which were published in 2002. These criteria include histopathology of minor salivary glands as one of the objective diagnosis criteria, even though biopsy results must be applied to the oral component and not the whole syndrome. The present study established the fact that Tarplay's scale was a reliable method to histologically assess labial salivary glands biopsies and to establish diagnosis of SS, since there is a direct association between obtained Tarplay's index and the possibility of suffering Sjögren's syndrome.

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