International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Clinical, Histopathological, and Serological Comparisons between Primary and Secondary Sjögren's Syndrome

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Abstract: ***This study compares the clinical, serological, and histopathological characteristics of primary Sjögren's Syndrome (pSS) and secondary Sjögren's Syndrome (sSS) in Iraqi patients. Conducted at Medical City Hospital / Baghdad over two years, it enrolled 218 pSS and 207 sSS patients. Key findings include significant differences in parotid gland enlargement, arthritis, and serological markers between the groups. These results highlight the distinct clinical profiles of pSS and sSS, contributing to better diagnostic and treatment approaches.***

Keywords: Sjogren's syndrome, primary Sjogren's syndrome, secondary Sjogren's syndrome, parotid gland enlargement, autoimmune disease

1. Introduction

Sjögren's Disease is an alternative name for Sjögren's Syndrome. Its use has been advocated by Sjögren's Foundation, in part due to concerns that "syndrome" implied to some a collection of nuisance symptoms rather than a distinct autoimmune disease with potentially serious outcomes [(1).]

Primary Sjogren's Syndrome [(2)] is a chronic autoimmune inflammatory connective tissue disorder which manifests as oral and ocular dryness, and parotid gland swelling caused by lymphocytic infiltration of exocrine glands and extra glandular involvement of various body systems includes Musculo - skeletal, skin, neurological, hematological, renal, pericardial, raynaud's phenomenon and fatigue.

SS when diagnosed alone is termed primary and when diagnosed in combination with another autoimmune disease like RA, SLE or systemic sclerosis is termed secondary. [(3)]

The histopathological changes in pSS is a focal infiltration of mononuclear inflammatory cells replacing the glandular epithelium of the exocrine gland. Prevalence studies of pSS showed different results between 0.04% to 4.8%. [(4)]

These studies were performed on various populations, using restricted age range of small sample size. Studies of SS used different classification criteria. Four main criterion sets were used for classification of SS [(5, 6, 7, 8)] also different methodologies were used in these studies.

In Iraq primary sjogren's estimated prevalence was 0.59% of adult population and was more common in elderly females. [(9)]

Aim of the study this study aims to compare the clinical, serological, and histopathological characteristics of primary and secondary Sjögren's syndrome in Iraqi patients.

This study is significant as it provides insights into the distinct clinical profiles of pSS and sSS, which can aid in improving diagnostic accuracy and patient management.

Patients and methods

Study design
This cross - sectional study was conducted among pSS and RA patients associated with SS (sSS) at the Rheumatology Unit of Baghdad Teaching Hospital / Medical City from January 2022 until December 2023.

Study population:

Inclusion criteria
Patients: the study was conducted in a tertiary care hospital provides regular follow - up care and treatment for patients with various rheumatic diseases.

Patients fulfilling the AECG - 2002 criteria [(10)] for classification of pSS (218 patients) and those fulfill the same criteria with a difference that anti - Ro/La antibodies are not a criterion for sSS (207 patients) whom presented with sicca - related manifestations in the context of Rheumatoid Arthritis, [(11)] were enrolled in the study.

Exclusion criteria
Patients had to take no medication that would reduce salivary flow like anti - histamine, beta blockers, diuretics or sedatives within 2 days before the study, no history of

hepatitis C or HIV infection, sarcoidosis, Lymphoma or history of neck/head radiotherapy.

Ethical approval
The study protocol was approved by supervising committee of Iraqi Board for Medical Specialization. A signed consent was obtained from each participant included in the study according to the declaration of Helsinki.

Data collection and entry
A questionnaire was used to collect information from all patients studied.

Socio - demographic and clinical characteristics:
All patients had a face - to - face interview by a rheumatologist using a standardized form that included questions about demographic data and use of medications. Full history was taken and complete clinical examination was made for all patients. In addition, to 6 - item screening questionnaire for oral and ocular symptoms [10] was applied, also Schirmer's test [10] and salivary flow rate test [12] were carried out.

Blood tests and investigations for antibodies were done for all patients.

Patients with negative tests for both anti - Ro and La serological markers were sent for labial salivary gland biopsy and results were sent for histopathological studies to confirm the diagnosis.

Statistical Analysis: Data were analyzed using EPI - INFO Version 6 for both student's t - test &Chi - square.

2. Results

Demographic characteristics of the patients

All together we studied 218 patients with pSS and 207 patients with sSS.

The mean patient's age was 51.7 ± 10.6 for PSS and 51.7 ± 10.55 for sSS. The female/male ratio was 9/1 for pSS and 8.3/1 for sSS, no differences were reported for age and sex of both groups of patients. All patients were presented clinically with dry eye and dry mouth which were confirmed by schirmer's test showing moderate reduction with a mean for pSS group of 3, 56 ± 1, 12 and for sSS group as 3.72 ± 1.22 without significant differences between the two groups, while the mean salivary flow rate in both groups showed a significant reduction, with a mean of 6.14 ± 2.69 in pSS and a mean of 5.97 ± 2.53 among sSS patients without significant differences between the two groups as shown in table (1).

Clinical manifestations of both studied groups (pSS, sSS) patients, the frequency of parotid gland enlargement were significantly higher among pSS compared to sSS group. Arthralgia/Arthritis were reported significantly higher among sSS compared to pSS group, while tooth decay were slightly higher among pSS compared to sSS without significant differences. Fatigue was reported higher among pSS compared to sSS group without significant differences. Lung involvement was found more frequently among pSS compared to sSS patients but without significant differences.

Raynaud's phenomenon was reported significantly higher among sSS compared to pSS patients.

Both hepatomegaly and splenomegaly were more frequently reported among pSS compared to sSS patients without significant differences between them. Lymphadenopathy was significantly more frequent among sSS compared to pSS patients. Vasculitis was slightly more reported upon pSS compared to sSS without significant differences. Polyneuropathy was significantly more frequent among pSS compared to sSS patients. Renal tubular acidosis was reported significantly more frequent among sSS compared to pSS patients.

Myositis, pericarditis and skin manifestations were rarely reported among patients in both studied groups without significant differences between them.

More detailed data about clinical manifestations were shown in table (2).

On comparing blood tests and histopathological changes between patients with pSS and those with sSS as shown in table (3), the number and percentage of patients with low Hb were significantly higher among sSS compared to pSS patients. While the number and percentage of patients with high ESR were higher among pSS compared to sSS but the differences were insignificant.

The number and percentage of positive RF were significantly higher among sSS compared to pSS patients.

The number and percentage of positive ANA were higher in pSS compared to sSS patients.

The number and percentage of patients with positive SSA among pSS were significantly higher compared to those of sSS patients, while the number and percentage of patients with positive SSB were higher among pSS patients compared to those of sSS, but the differences were insignificant.

Histopathological findings
Labial salivary gland biopsies were performed for 149 patients with negative serology (53 of pSS and 96 of sSS) patients and sent for histopathological studies.

No immunohistochemically assay were done for the lip biopsies because of it is unavailability in our laboratories. Among lip biopsies of 53 pSS patients 23 showed nonfocal lymphocytic infiltration and 30 showed focal lymphocytic infiltration, while of the the 96 sSS patients lip biopsies 41 showed nonfocal and 55 showed focal lymphocytic infiltration, the results were comparable between both groups.

Lymphoma: was reported in two out of 218 pSS patients studied while it was not reported among any of sSS patients.

Table 1: Comparison of mean values of Schirmer's test and mean values of salivary flow rate between patients of primary and secondary Sjogren's syndrome.

Test	Group	No. of Patients	Mean ± SD	t - test, P - Value
Schirmer's test/ml - s/min	Primary S. S	218	3.56 ± 1.12	1.99, 0.15
	Secondary S. S	207	3.72 ± 1.22	
Salivary flow - ml/5 min	Primary S. S.	218	6.14 ± 2.69	0.45, 0.502
	Secondary S. S.	207	5.97 ± 2.53	

Table 2: Comparison of Clinical manifestations between patients of (Primary & Secondary Sjogren's syndrome)

Variables	Primary S. S (n= 218) No. (%)	Secondary S. S (n= 207) No. (%)	Chi - Square, P - vale
Parotid Enlargement	71 32.56	20 9.66	21.73, =0.0000031
Arthralgia/Arthritis	53 24.31	207 100	64.5, < 0.000001
Tooth Decay	126 57.79	124 59.90	0.5, >0.05
Fatigue	39 17.89	31 14.97	0.47, >0.05
Lung Involvement	15 6.88	7 3.38	2.39, >0.05
Reynaud's Phenomena	13 5.96	35 16.9	10.12, = 0.00146
Hepatomegaly	10 4.58	8 3.38	0.13, >0.05
Splenomegaly	8 17.44	4 8.28	1.51, >0.05
Lymphadenopathy	6 13.08	15 31.05	4.13 = 0.042
Vasculitis	6 2.75	4 1.93	0.3, >0.05
Polyneuropahy	18 8.25	8 17.44	4.13 = 0.042
Renal	2 0.92	8 3.86	3.83, =0.05
Myositis	2 0.92	0 0	1.89, >0.05 Mant Hanz*
Pericarditis	3 6.54	3 1.45	0.12, >0.05 Yate Cor*
Skin Manifestation	7 3.21	5 2.41	0.23, >0.05 Mant Hanz

No. =Number (%) =Percent *Yate & Mantil Haenszel Correction

Table 3: Comparison of laboratory parameters between two groups (Primary & Secondary Sjogren's syndrome).

Variables	Primary S. S (n= 218) No. %	Secondary S. S (n= 207) No. %	Chi - Square, P - vale
Low Hb%	122 55.96	188 90.82	10.28, = 0.00134
High ESR	168 77.06	193 93.23	1.77, >0.05
RF Positive	118 54.12	186 89.85	11.11 =0.00086
ANA Positive	79 36.23	66 31.88	0.44, >0.05
SSA Positive	64 29.35	33 15.95	6.86, =0.00885
SSB Positive	31 14.22	28 13.52	0.03, >0.05

3. Discussion

{Fourty years ago the term primary and secondary sjogren's syndrome (p+s SS) were used ([13]). Patients with SS alone presented more frequently with recurrent parotid gland enlargement, higher prevalence of oral symptoms, purpura, lymphadenopathy, myositis and renal involvement compared to those with SS in a RA background (RA/SS) ([14]) which display more frequently severe arthritis, anemia, lung involvement and radiological joint damage ([15]). Patients with SS alone exhibited increased frequency of anti - RO/SSA and LA - SSB antibodies. ([10]) }
This study showed similarities and differences between patients with PSS and those with sSS as reported in the three tables in the results of the study earlier.

Parotid gland enlargement and higher frequency of oral symptoms were reported significantly more frequently among PSS compared to sSS, this finding is in agreement with other study. ([21])

The differences between our study findings and previous studies are attributed to different study population, different classification criteria used in each study. The standard of education and understanding of the questionnaire, the possibility of genetic predisposition …… Primary and secondary SS should be replaced by more descriptive terminology: SS when the disease is expressed as an entity alone or SS associated with systemic or organ specific autoimmune disease, provided in all uses the recently published set of criteria for SS are fulfilled ([10]). Indeed, in the later, the term secondary is no longer exist and the presence of an underlying autoimmune disease dose not exclude the classification of pSS, once the proposed criteria are fulfilled. ([10])

Recurrent parotid gland swelling is frequently reported in 71 patients of our study a finding is in agreement with other author (Ramos - Casals M,) ([16]). Tooth decay were highly reported among our studied patients (126) which is higher than what was reported by other author ([16]) of one - third of studied population.

Fatigue was reported in 83 of our pSS patients which is in agreement with 70 - 80% of Negrini S. ([17]) studied patients.

Arthralgia/arthritis were reported among 53 of 218 of our patients with pSS which was much more when compared to 45% of 419 patients (Fauchais Al, [18]).

We reported poly neuropathy central and peripheral among 18 out of our 218 pSS patients. Nervous system involvement can be seen in up to 20% of pSS Sjogrens Syndrome may affect both central and peripheral nervous system (Brito - Zeron P[19]) which are very much comparable.

Pulmonary involvement was reported among 15 of 218 pSS patients in our study.

While the estimated prevalence of pulmonary involvement is between 9 and 24% (Stojan G[20]).

Extra glandular manifestations were similar in both groups, but Raynauds phenomenon was more common in sSS (41% vs.16%) in pSS in Hernandez - Molina G, [21] study.

And was reported in sSS 17% vs.6% in pSS in our study

Renal involvement: In our study was reported more among sSS 8 patients compared to 2 pSS patients, while it was reported approximately in 5% of patients with SS by another author. [22]

Serological markers of ANA and RF were positive.

All tested serological markers showed higher prevalence among pSS compared to sSS patients as shown in table (3), except Rheumatoid factor which was lower among pSS compared to sSS.

[Lip biopsies were done for 149 SS patients 53 of pSS and 96 of sSS, the prevalence of focal 75% and nonfocal 25% lymphocytic infiltration in both varieties of SS was identical]

Lymphoma: Two patients of PSS developed lymphoma during the course of their illness. Non - hodgkins lymphoma occurs in approximately 2 - 9% of patients with PSS as reported by another author. (Voulgarelis M). [23]

4. Conclusions

This study highlights the clinical, serological, and histopathological differences between pSS and sSS in Iraqi patients. Findings such as higher rates of parotid gland enlargement in pSS and significant arthralgia in sSS underline the importance of tailored diagnostic criteria and treatment approaches for these conditions.

Conflict of interest: The Authors declare no conflict of interest.

Acknowledgments: Grateful thanks are due to Professor Jamal Rasheed AL - Rawi for doing the statistics of the study, to all patients enrolled in the study for their good cooperation and to Harith Ahmed, Pharmacist for much help in typing the manuscript and to Alfarouk Shafeek, University student and Shahad Shafeek, Medical student for much effort and help during manuscript preparation.

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