Reumatol Clin. 2010;**6(6)**:299-302

Reumatología Clínica

www.reumatologiaclinica.org

Brief original

Frequency of systemic manifestations in patients with primary Sjögren's syndrome in Argentina

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ARTICLE INFO

Article history:
Received July 13, 2009
Accepted January 14, 2010

Keywords:
Sjögren's Syndrome
Autoimmunity
Connective Tissue Diseases
Xerostomia

ABSTRACT

Twenty to 71% of patients with Sjögren's syndrome (SS) will develop systemic manifestations.
Objetive: To characterize the clinical-serological presentation and the frequency of systemic manifestations in patients with primary SS.
Methods: Retrospective study including patients with SS visited in "Hospital Británico de Buenos Aires" during the period from January 2000 to August 2008.
Results: Forty-one patients fulfilled the 2002 American-European classification criteria for SS. All patients were women. Mean age at enrollment was 57,85±12,42 years (range 26-79). Mean duration of the disease was 9,28 years (range 0,08-24). Thirty-three (80.49%) developed systemic manifestations. The most frequent were arthritis, cutaneous vasculitis and polyneuropathy. This group featured more frequently ANA titles ≥1/640 and hypocomplementemia; although no statistical significance was found. The frequency of systemic manifestations found was greater than reported in the literature.
Conclusions: A multidisciplinary approach focusing also on systemic manifestations should be the new standard for management of SS.

Palabras clave:
Síndrome de Sjögren
Autoinmunidad
Enfermedades del tejido conectivo
Xerostomía

Frecuencia de manifestaciones sistémicas en pacientes con síndrome de Sjögren primario en Argentina

RESUMEN

Del 20-71% de los pacientes con síndrome de Sjögren (SS) desarrolla manifestaciones sistémicas.
Objetivos: El objetivo fue evaluar las características clinicoserológicas y frecuencia de manifestaciones sistémicas en pacientes con SS primario.
Material y métodos: Estudio retrospectivo con revisión de historias clínicas de pacientes con Sd de Sjögren primario visitados en el Hospital Británico de Buenos Aires en el período desde Enero de 2000 a Agosto de 2008.
Resultados: Se incluyeron 41 pacientes que cumplían criterios de clasificación Europeoamericanos 2002 para SS, todos de sexo femenino. La edad media fue 57,85 ± 12,42 años (rango 26-79). El tiempo de evolución fue de 9,28 años (rango 0,08-24). Treinta y tres (80,49%) presentaron manifestaciones sistémicas. Las más frecuentes fueron artritis, vasculitis cutánea y polineuropatía. Este grupo presentó más frecuentemente títulos de AAN ≥ 1/640 e hipocomplementemia; aunque no estadísticamente significativas. La frecuencia de manifestaciones sistémicas halladas fue mayor a la reportada en otras series.
Conclusiones: Un abordaje multidisciplinario enfocado en las manifestaciones sistémicas debería ser el nuevo estándar para el manejo del SS.

Introduction

Sjögren's Syndrome (SS) is a chronic autoimmune disease characterised by T and B lymphocyte overexpression that mainly affects the exocrine glands and can clinically express itself in different ways.[1-3] The variety of ways it can appear can significantly delay its diagnosis.[4] Some patients present the glandular form of this disease, characterised by dry mucous membranes and skin (sicca syndrome), while others show extra glandular compromise. According to the series, 20%-71% of patients develop systemic manifestations[3,5]; these, defined as organ and non-exocrine tissue compromise, are present

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in a considerable number of patients[6] and include skeletal muscle, skin, respiratory, gastro-intestinal, nephro-urological, neurological, psychiatric, endocrine, and haematological manifestations.

The heterogeneous expression of these systemic manifestations and better knowledge of SS pathophysiology has prioritised its importance and early diagnosis in the last few years.[7] Despite this, diagnosis still takes a long time, because the systemic manifestations are normally underestimated, not only by patients but also by doctors.[8] The objective was to characterise the clinical and serological presentation and the frequency of systemic manifestations in a group of patients with primary Sjögren's Syndrome.

Materials and methods

The patients with primary SS included were those visiting the rheumatology department at the "Hospital Británico de Buenos Aires" between January 2000 and August 2008. Their clinical histories were retrospectively studied according to a predefined protocol, and data regarding demographic variables and clinical facts was recorded.

Eye manifestations such as xerophthalmia were recorded (if the patient referred to a gritty sensation, dryness in the eyes over the last 3 months, or the need to use eye drops at least three times a day). It was considered that the patient showed signs of dry eyes when she or he had at least one of the following: Schirmer test less then 5mm in 5 min, Rose Bengal test greater than 4 according to the Van Bijsterveld classification, and/or pre-corneal film break-up time of less than 10s. It was considered xerostomia when the patient felt that he or she had had a dry mouth over the last 3 months, persistent inflammation of the salivary glands, or the need to drink large amounts of liquids when eating. Salivary flow test, salivary scintigraphy, and parotid gland scans are not carried out by us frequently; this is why they were not taken into account.

The minor salivary gland biopsy was considered positive with a Chisholm score greater than or equal to an area (grades 3-4) of 50 lymphocytes in 4 mm^2.

Manifestations due to SS were recorded: among them, the presence of xeroderma (skin dryness); arthritis (defined as non-erosive synovitis confirmed by a doctor); Raynaud's phenomenon (defined as the presence of colour changes in distal vascular beds characterised by paleness and/or cyanosis plus erythema); cutaneous vasculitis (confirmed by a skin biopsy in all cases); xerotrachea (defined as a dry cough present for at least 3 months); interstitial pulmonary compromise (characterised by a high resolution CAT scan assessed by a pneumologist specialising in interstitial pathology); chronic atrophic gastritis or lymphocytic colitis (assessed with a digestive video-endoscopy biopsy); xerovagina (characterised by vaginal dryness or dyspareunia assessed by a gynaecologist); interstitial cystitis (assessed by a cystoscopy); renal compromise (assessed by a renal biopsy with a needle guided by tomography); and CNS organic compromise (assessed by a brain MR with angioresonance) and peripheral organic compromise (assessed by electromyography and somatosensory evoked potentials).

Associated clinical data that was not directly due to SS was also recorded, such as psychiatric compromise, cognitive deterioration, and endocrinopathies.

The laboratory recorded the presence of: rheumatoid factor through positive nephelometry to a value of ≥12 UI/ml, positive Ac anti-nuclear antibodies (ANA) to a titre ≥1/160 detected through indirect immunofluorescence using HEp-2 cells, Ac anti-SS-A/Ro, and anti-SS-B/La through ELISA with a positive cut-off value of ≥12 UI/ml. Serum cryoglobulin detection was carried out by cryocrit. The presence of paraproteins was determined for immunoelectrophoresis and complementary levels (C3 and C4) were determined through nephelometry. Detection of HBV and HCV was carried out through ELISA.

Data recording was carried out according to procedures recommended by the institutional revision committee of the "Hospital Britanico." For age, the results were informed as the mean +SD. The confidence interval (CI) was calculated at a value of 95%. The Mann-Whitney test was applied for continuous variables and χ^2 or exact Fisher test for categorical variables. The value of $P<.05$ was taken to indicate statistical significance. The statistical analysis was carried out using the "Intercooled STATAS 10.0" programme.

Results

Forty-one patients (all female) who complied with 4 or more of the classification criteria proposed for SS by the European-American consensus[9] were analysed. The mean age was 57.85±12.42 years (range, 26-79 years). The time of evolution was 9.28 years (range, 0.08-24 years) from the date of diagnosis to the date of inclusion. Minor salivary gland biopsy was carried out on 16 patients and was positive in 12 (75%). The scoring for Lymphocyte location was level 4 in 7 patients and 3 in 5 patients. The score value for location did not vary significantly with the presence of systemic manifestations.

Table 1
Glandular manifestations and laboratory findings in 41 patients with primary Sjögren's syndrome

Manifestations	% (No.)
Xerophthalmia	100 (41)
Schirmer test	87.80% (36)
Rose Bengal	65.85% (27)
Break-up time	56.10% (23)
Xerostomia	95.12% (39)
Recurrent sialadenitis	29.27% (12)
RF	51.21% (21)
ANA	73.17% (30)
ANA titre ≥1/640	43.90% (18)
Anti-Ro/SS-A	90.24% (37)
Anti-La/SS-B	65.85% (27)
Cryoglobulinemia	9.76% (4)
Hypocomplementemia	21.95% (9)
Hypergammaglobulinemia	58.54% (24)

ANA indicates anti-nuclear antibodies; RF, rheumatoid factor.

Table 2
Systemic manifestations and associated disorders in 41 patients with primary Sjögren's syndrome

Systemic manifestations	No. (%)
Total	33 (80.49)
Arthritis	15 (36.58)
Xeroderma	8 (17.07)
Raynaud's phenomenon	8 (17.07)
Cutaneous vasculitis	10 (24.39)
Xerotrachea	12 (29.27)
Interstitial pulmonary disease	2 (4.88)
Oesophageal dysmotility	9 (21.95)
Chronic atrophic gastritis	6 (14.63)
Lymphocytic colitis	1 (2.44)
Glomerulonephritis	1 (2.44)
Interstitial nephritis	1 (2.44)
Interstitial cystitis	2 (4.88)
Cognitive deterioration	4 (9.76)
MS-type lesions	1 (2.44)
Polyneuropathy	10 (24.39)
Psychiatric disorders	17 (41.46)
Hypothyroidism	17 (41.46)
Autoimmune thyroiditis	4 (9.76)

MS indicates multiple sclerosis.

Table 3
Comparison between patients with systemic manifestations and without systemic manifestations in 41 patients with primary Sjögren's syndrome

Characteristics	Group with systemic manifestations (n=33)	Group without systemic manifestations (n=8)	Significance
Age when diagnosed	49.71 (13)	52.57 (13)	*P*=.53
Average time of evolution	7.5 years (range=1-24)	4 years (range=1-22)	*P*=.29
Positive ANA	25 (75.76%)	5 (62.50%)	*P*=.44
Titre ≥640	16/25	1/5	*P*=.07
Anti-Ro/SS-A	29 (87.88%)	8 (100%)	*P*=.30
Anti-La/SS-B	22 (66.67%)	5 (62.50%)	*P*=.56
RF	17 (51.51%)	4 (50%)	*P*=.62
Hypergammaglobulinemia	20 (60.61%)	4 (50%)	*P*=.58
Hypocomplementemia	9 (27.27%)	0	*P*=.09
Cryoglobulinemia	4 (12.12%)	0	*P*=.30

ANA indicates anti-nuclear antibodies; RF, rheumatoid factor.

Table 1 shows glandular manifestations together with findings from the laboratory.

Thirty-three patients (80.49%: CI: 65.13-91.18) presented systemic manifestations. Some presented more than one manifestation. The most frequent were: non-erosive arthritis in 15 patients (36.58%); xerotrachea in 12 (29.27%); cutaneous vasculitis in 10 (24.39%), 9 of which were a leukocytoclastic type and 1 lymphocytic; and polyneuropathy in 10 (24.39%), 5 of a sensory type, 3 a motor type, and 2 were sensorimotor. Less frequently observed were: Raynaud's phenomenon in 8 (17.07%); xerovagina in 8 (17.07%); interstitial pulmonary disease in 2 (4.88%), in the form of unspecific interstitial pneumonia and common interstitial pneumonia; renal compromise in 2 (4.88%), characterised by interstitial nephritis and membrane glomerulonephritis respectively; interstitial cystitis in 1 (2.44%); lymphocytic colitis in 1 (2.44%); peripheral nervous system compromise in the form of polyradiculoneuritis in 2 (4.88%) and multiple mononeuritis in 1 (2.44%); and CNS compromise characterised by multiple sclerosis (MS)-type demyelinating lesions in RMen1 (2.44%) (Table 2).

Regarding serological manifestations, 37 (90.24%) were positive for Ac anti-Ro/SS-A; 27 (65.85%) for anti-La/SS-B; 30 patients (73.17%) presented ANA, 26/30 having a mottled pattern; 21 patients (51.21%) were positive for the rheumatoid factor; and18 (43.90%) showed figures of ANA ≥1/640. In 24 patients (58.54%) hypergammaglobulinemia was observed. In 9 patients (21.95%) hypocomplementemia was found, and in 4 (9.76%) cryoglobulinemia, although these determinations were only carried out in the case of cutaneous vasculitis or nervous system compromise. In 4 patients (9.76%) positive Ac anticardiolipin was detected but none presented the thrombotic events associated with it. No patient developed lymphoproliferative disease or monoclonal forms.

All patients were negative for HCV and 1 presented HBV 14 months after diagnosis with SS.

Table 3 presents the comparison between patients with and without systemic manifestations.

As a discovery, the presence of psychiatric disorders was recorded in 17 patients (41.46%), with depression being the most frequent (15 patients) and in 4 cases (9.76%), cognitive deterioration. Endocrine disorders were also recorded, among which there were 17 patients (41.46%) with hypothyroidism, 4 patients (9.76%) with autoimmune thyroiditis, and 2 (4.88%) with DM. A patient presented primary biliary cirrhosis 2 years after being diagnosed with SS.

Discussion

In SS, the local inflammatory response is the origin for the soluble mediators responsible for systemic manifestations. The persistent activation of B Cells is considered the main characteristic of this pathology.[10] The production of autoAc and hypergammaglobulinemia represent the serological correlation of this phenomenon, while cutaneous vasculitis, renal compromise, and the compromise of the nervous system are clinically related manifestations.[3] The presence of hypocomplementemia, type II cryoglobulinemias, cutaneous vasculitis, and persistent parotid tumefaction precede the development of lymphoproliferative diseases and lead to a worse prognosis.[11] Adopting the concept that SS is an autoimmune organ-specific pathology, which subsequently expands into a systemic disease, is to have a limited vision of the problem.[12]

In this series of cases, the frequency of systemic manifestations found (80.49%) was greater than that reported in other series[3,5,13,14] and, although it did not reach statistical significance, it was observed in a group of patients where the disease had evolved over a longer period, and could be associated to a sustained stimulation of B lymphocytes.

The majority of patients with SS show ANA in serum, with a mottled pattern being the most common[15] just as in our group. In this series, the patients with systemic manifestations frequently recorded titres higher than 1/640. High ANA figures could be associated to systemic manifestations. Ramos-Casals et al,[13] as well as Asmussen et al,[14] drew attention to the association of titres to ANA, together with the presence of skin pupura, myositis, Raynaud's phenomenon, and lymphopenia; others communicated that their presence (with titres ≥1/100) was associated with a greater level of lymphocytic infiltration in the salivary biopsy.[16] The majority of systemic manifestations mentioned have a prognosis value and are not included in the 2002 diagnosis criteria.

In our series, hypocomplementemia tended to be more frequently observed in the group with systemic compromise, but the difference was not statistically significant. A rheumatoid factor has been observed in approximately 50% of the patients with SS; this is similar to the results in this series, although its presence was not associated to systemic manifestations.

This study's main limitation was that the data was taken retrospectively. It is possible that in an evolving series, some systemic manifestations would have been considered to have been caused by different things than SS, and the scarcity in numbers for the series could possibly have resulted in insufficient means for detecting differences between the groups for some variables.

To summarise, a series of patients with Sjögren's syndrome was presented, who showed a high frequency of systemic manifestations, which supports the hypothesis that it is a systemic disease rather than an organ-specific one. Although some serological manifestations were observed more frequently in the group of patients with systemic manifestations, greater patient numbers are required to evaluate these associations. At present, a multidisciplinary approach should be carried out, focused not only on glandular manifestations, but also on systemic manifestations. In this way, treatment would be improved.

Conflict of interest

The authors declare no conflict of interests.

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