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Original article

Elderly onset of primary Sjögren's syndrome: Clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients

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ABSTRACT

Objectives: To study and compare the clinical and serological features of patients with elderly versus adult and younger onset of primary Sjögren's syndrome (pSS).
Methods: We analyzed retrospectively 336 consecutive pSS patients followed at our unit. They were subdivided into three groups according to the age at disease onset: elderly (> 65 years), adult (> 40 and ≤ 65 years), and young (≤ 40 years). Clinical and immunological features of the disease, labial salivary glands biopsy, ocular and oral tests were collected at time of diagnosis and then compared among the three groups.
Results: In 21 (6%) patients, disease onset occurred after the age of 65 years. At the time of diagnosis, 15 (71.4%) of these patients reported symptoms of dry mouth and 16 (76.1%) of dry eye. The most common extraglandular manifestation were arthralgias in 14 (66.7%), Raynaud's phenomenon in five (23.8%) and purpura in three (14.2%) cases. Ocular diagnostic tests (Schirmer's I and Rose-Bengal staining) were positive respectively in 17 (80%) and nine (44.4%) patients. In eight (38%) cases, unstimulated whole salivary flow showed normal values, while 12 patients (57.1%) showed positivity for salivary sialography. A focus score greater or equal to 1 per 4 mm^2 was demonstrated in 11 (53.3%) of the 21 cases.
Conclusion: Elderly onset of pSS was associated with similar incidence of the diagnostic tests positivity (parotid sialography, ocular tests, minor salivary gland biopsy) in comparison with adult and younger onset. Moreover, no statistical differences were found among the three groups concerning sex, disease duration, as well as ocular and oral symptoms.

1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy characterized by dryness of eyes (keratoconjunctivitis sicca) and mouth (xerostomia) as well as recurrent parotid gland swelling. The spectrum of SS extends from an organ-specific autoimmune disorder (autoimmune exocrinopathy) to a systemic process that may involve the musculoskeletal, pulmonary, gastrointestinal, hematologic, vascular, dermatologic, renal, or nervous systems [1–3]. SS can occur alone (primary) or in association with another autoimmune rheumatic disease (secondary). Primary SS (pSS) affects 0.3–5% of the population, the proportion being determined by the age group studied and by the diagnostic criteria used [4,5]. The disease can occur in patients of all ages, but mainly affects women in the forth and fifth decade of life, with a female:male ratio of 9:1 or even more [4].

Several investigators have reported that age at onset has a modifying effect on disease expression of some autoimmune diseases, such as systemic lupus erythematosus (SLE) [6,7] and rheumatoid arthritis (RA) [8]. In SLE, certain clinical features usually associated with severity, such as nephropathy, are less common in patients with an older onset [7] and serological abnormalities have also been reported to be different in elderly patients [7,9,10]. Also in pSS, juvenile (< 16 years) and young (< 35 years > 16) onsets of the disease have been associated with distinctive clinical or immunological characteristics [11,12]. To our knowledge, only few studies have been published so far on the clinical and immunological features of pSS in the elderly [13,14].

To better determine whether any relation exists between disease manifestations and age at onset, we analyzed, in a series of 336 unselected patients, clinical manifestations and immunoserologi-

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cal findings of patients with an elderly age at onset (age ≥ 65 years) in a retrospective designed study.

2. Methods

Three hundred and twenty-two female and 14 male outpatients with pSS consecutively attending our Rheumatologic Unit between May 1990 and December 2007 were studied retrospectively. The mean age and disease duration (time from onset of symptoms at the time of the diagnosis) were (M ± SD): 47.8 ± 14.5 years, range: 17–84 years and 4.3 ± 3.0 years, range: 1–22 years, respectively. The mean follow-up duration (time from the diagnosis up to the start of the study) was (M ± SD): 12.2 ± 7.1 years, range: 1.1–22 years.

Onset of the disease was defined as the first subjective experience of the symptoms described in any of the items of the classification criteria [15] or as the presence of arthritis, arthralgias, elevated longstanding erythrocyte sedimentation rate (ESR) without any other obvious cause, peripheral neuropathy, longstanding fever without infection, or excessive chronic fatigue leading to medical examination.

Patients with pSS were classified into three groups according to the age at disease onset: elderly group (> 65 years), adult group (> 40 and ≤ 65 years), and young group (≤ 40 years). The age limit was established arbitrarily. All patients were Caucasians and fulfilled four or more of the classification criteria for pSS proposed by the European–American Consensus Conference [15]. Moreover, the presence of either a positive minor salivary gland biopsy (focus score ≥ 1) or a positive immunological test (autoantibodies anti-Ro and/or anti-La) was required for the diagnosis. None of these patients presented clinical or immunological evidence of other systemic autoimmune disease, hepatitis C virus infection, isolated keratoconjunctivitis sicca, or were taking medications that might induce sicca syndrome.

Signs and symptoms were collected at the time of diagnosis. Clinical examination included recurrent parotid or sub-mandibular gland swelling, and current sicca symptoms of eyes and mouth. Xerostomia was defined as a subjective troublesome daily feeling of dry mouth for more than 3 months. Special attention was focused on possible non-exocrine organ involvement of pSS: arthritis, defined as swollen and tender joints observed by the examining doctor; renal involvement, including interstitial nephritis and glomerulonephritis, documented by renal biopsy; pulmonary involvement, including small airway disease or interstitial lung disease, defined by computer tomography (CT) scan and pulmonary function tests, and purpura by a history of typical episodic palpable purpuric lesions in the lower limbs or by skin biopsy. Enlargement of the liver or spleen was confirmed by ultrasound. Autoimmune thyroiditis was diagnosed by the presence of anti-thyroid antibodies, and abnormalities on glandular sonography. Lymphadenopathy was defined as lymph node enlargement so persistent as to indicate a nodal biopsy in the opinion of the caring clinicians. Peripheral neuropathy was documented by nerve conduction studies in patients with clinical symptoms or signs suggestive of neuropathy. Diagnosis of lymphoma and other clinically significant lymphoproliferative disorders as well as other neoplastic diseases were supported by biopsy.

Salivary and ocular tests were carried out at the time of diagnosis. Salivary flow rates were determined by unstimulated whole salivary flow (positive: ≤ 1.5 mL in 15 min) according to the European–American criteria [15] and parotid sialography (positive: grade ≥ 1), according to Rubin and Holt [16].

A tear fluid secretion less or equal to 5 mm/5 min on Schirmer's I test was defined as abnormal. Rose-Bengal test was performed by the application of 1% solution of Rose-Bengal dye and by evaluating abnormal staining at the interpalpebral area of the cornea and conjunctiva with a slit lamp [17]. Keratoconjunctivitis sicca was established when either a decreased Schirmer I or an abnormal Rose-Bengal staining were present in at least one eye.

A biopsy from the minor salivary glands of the lower lip has been performed in 285 patients at the time of diagnosis, and was evaluated with focus scoring according to the American–European criteria [15]. Focus is defined as an aggregate of 50 or more mononuclear cells per 4 mm^2 and biopsy is positive when a focus score greater or equal to 1 per 4 mm^2 is present. Antinuclear antibodies (ANA) were determined by indirect immune-fluorescence on multi-block cryostat sections comprising rat liver and mouse kidney or with Hep-2 cells. A titre of 1:80 or more was regarded as significant. Antibodies to extractable nuclear antigens, including anti-ribonucleoprotein, anti-Sm, anti-Ro, anti-La, and anti-Scl 70, were measured by enzyme immunoassay. Complement levels (C3 and C4) and rheumatoid factor were measured by laser nephelometry. Hypergammaglobulinemia was defined as a total gamma globulins greater than 2 g/L. Serum β2 microglobulin was determined by radioimmunoassay (normal values: 1.0–2.5 mg/L), serum cryoglobulins (monoclonal or polyclonal) were detected after centrifugation: serum supernatant was removed, incubated at 4 °C for 8 days and examined for cryoprecipitate. Finally, hematologic abnormalities such as anaemia (Hb < 12 g/dL), excluding anaemia due to other causes such as hereditary hemoglobinopathies and iron deficiency, leukopenia (white blood cells [WBC] < 4,500/mm^3) and thrombocytopenia (platelets < 150,000/mm^3) were also assessed.

At the time of diagnosis, none of the patient took steroids, immunosuppressive drugs or drugs that could induce xerostomia.

Statistical analysis: prior to the examination, hematological and immunological data as well as oral/ocular test were dichotomized in positive and negative values. The comparison of categorical variables was performed using Khi^2 test. The Kruskal-Wallis test and subsequently the Dunnett post hoc test, were used for the comparison of continuous variables. A *P*-value < 0.05 was considered significant. Statistical analyses were performed using SPSS 11.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Demographic characteristics and clinical manifestations, immunohaematological profile as well as ocular and salivary involvement of elderly onset pSS patients are shown in Tables 1, 2 and 3 along with those of patients with adult and young disease onset.

In 21 (6%) patients, disease onset occurred after the age of 65 years. In this group, 20 (95%) were female and one (5%) male. At the time of the study, 15 (71.4%) of these patients reported symptoms of dry mouth and 16 (76.1%) of dry eye. The most common extraglandular manifestation were arthralgias in 14 (66.7%), Raynaud's phenomenon in five (23.8%) and purpura in three (14.2%) cases. Peripheral neuropathy, renal tubular acidosis with interstitial nephritis and interstitial lung disease were each found in only one patient. Two other patients (9.5%) had monoclonal gammopaty of uncertain significance (MGUS). Arthritis was documented only in one patient (4.8%) in which a symmetrical, non-erosive polyarthritis was present. Systemic symptoms such as asthenia and fever were reported by 10 (47.6%) and four (19%) patients respectively.

Ocular diagnostic tests (Schirmer's I and Rose-Bengal staining) were positive respectively in 17 (80%) and nine (44.4%) patients. In eight (38%) cases, unstimulated whole salivary flow showed normal values, while 12 patients (57.1%) showed positivity for salivary

Table 1
Demographic characteristics and clinical manifestations in patients *n*, (%) with primary Sjögren's syndrome at the time of diagnosis with reference to the age at onset: elderly (> 65 years), adult (> 40 and ≤ 65 years) and young patients (≤ 40 years).

Demographic characteristics				
	Elderly onset (*n* = 21)	Adult onset (*n* = 185)	Young onset (*n* = 130)	*P value*
Female, *n* (%)	20 (95)	175 (95)	127 (98)	*P* > 0.05
Mean ± SD age at onset (years)	72.9 ± 3.8	51 ± 6.7	28.5 ± 9.9	
Mean ± SD age at the diagnosis (years)	75.6 ± 4.7	54.9 ± 7.6	33.3 ± 8.3	
Mean ± SD disease duration (years)	9.7 ± 3.4	11.4 ± 4.1	13.8 ± 6.2	*P* > 0.05
Clinical manifestations				
Asthenia	10 (47.6)	113 (61.1)	83 (63.9)	*P* > 0.05
Fever	4 (19.1)	32 (17.2)	25 (19.2)	*P* > 0.05
Arthralgia	14 (66.7)	154 (83.2)	96 (73.9)	*P* > 0.05
Arthritis	1 (4.8)	56 (30.3)	48 (36.9)	*P* > 0.05
Raynaud's phenomenon	5 (23.8)	52 (28.1)	34 (26.1)	*P* > 0.05
Lymphadenopathy	3 (14.2)	29 (15.6)	28 (21.5)	*P* > 0.05
Purpura	3 (14.2)	32 (17.2)	29 (22.3)	*P* > 0.05
Hepatic involvement	1 (4.7)	10 (5.4)	6 (4.6)	*P* > 0.05
Peripheral neuropathy	1 (4.7)	5 (2.7)	1 (0.7)	*P* > 0.05
Interstitial pneumopathy	1 (4.7)	3 (1.6)	1 (0.7)	*P* > 0.05
MGUS[a]	2 (9.5)	10 (5.4)	1 (0.7)	*P* > 0.05

[a] Monoclonal gammopaty of uncertain significance.

Table 2
Number (*n*) and percentage of patients (%) with primary Sjögren's syndrome at the time of diagnosis with haematologic and immunologic disorders with reference to the age at onset: elderly (> 65 years), adult (> 40 and ≤ 65 years) and young patients (≤ 40 years).

	Elderly onset (*n* = 21)	Adult onset (*n* = 185)	Young onset (*n* = 130)	*P value*
Anaemia (Hb < 12g/dL)	6 (28.5)	52 (28.1)	36 (27.6)	*P* > 0.05
Leukopenia (WBC < 4,000/mm^3)	4 (19)	46 (24.8)	29 (22.3)	*P* > 0.05
Thrombocytopenia (PLT < 100,000/mm^3)	2 (9.5)	22 (12.1)	9 (7.1)	*P* > 0.05
ESR > 20 mm 1st h	10 (47.4)	99 (54.1)	80 (63.5)	*P* > 0.05
Rheumatoid factor > 40 IU/L	15 (71)	123 (67.8)	95 (75.8)	*P* > 0.05
C3 < 50mg/dL	3 (14.3)	24 (12.8)	30 (22.9)	*P* > 0.05
C4 < 20mg/dL	4 (19)	35 (18.9)	31 (23.8)	*P* > 0.05
ANA positive (titre > 1:80)	18 (85.7)	153 (87.9)	117 (92.8)	*P* > 0.05
Anti-Ro+	14 (66.7)	131 (71.4)	109 (83.9)	*P* > 0.05
Anti-La+	11 (52.3)	96 (51.8)	82 (63)	*P* > 0.05
Hypergammaglobulinemia (γ-globulins > 2g/L)	10 (47.6)	120 (64.8)	90 (69.2)	*P* > 0.05
Cryoglobulins	1 (4.7)	8 (4.3)	2 (1.5)	*P* > 0.05
Serum β2 microglobulin > 2.5mg/L	1 (4.7)	14 (7.5)	8 (6.1)	*P* > 0.05
Anti-thyroid antibodies	2 (9.5)	39 (21)	19 (14.7)	*P* > 0.05

sialography. A focus score greater or equal to 1 per 4 mm^2 was demonstrated in 11 (53.3%) of the 21 cases.

Immunological features were as follows: ANA were positive in 18 (85.7%), rheumatoid factor in 15 (71.1%), anti-Ro in 14 (66.7%), anti-La in 11 (52.3%), cryoglobulins in one (4.7%) patients. Low C4 (< 20 mg/dL) was found in four (19%) cases. No patient had positive anti-dsDNA or anti-Sm antibodies.

No statistical differences were found between the three groups of pSS patients concerning sex and disease duration, ocular and oral symptoms.

Table 3
Ocular and oral involvement in patients *n*, (%) with primary Sjögren's syndrome at the time of diagnosis according to the age at onset: elderly (> 65 years), adult (> 40 and ≤ 65 years) and young patients (≤ 40 years).

	Elderly onset (*n* = 21)	Adult onset (*n* = 185)	Young onset (*n* = 130)	*P value*
Glandular signs and symptoms				
Dry mouth	15 (71.4)	158 (85.9)	94 (72.3)	*P* > 0.05
Dry eyes	16 (76.1)	150 (81.6)	102 (78.5)	*P* > 0.05
Parotid swelling	3 (14.2)	39 (21)	31 (23.8)	*P* > 0.05
Ocular tests[a]				
Schirmer I test (≤ 5 mm in 5 min)	17 (80)	149 (80.5)	86 (66.1)	*P* > 0.05
Rose-Bengal (score ≥ 4 according to van Bijsterveld's scoring system)	9 (44.4)	72 (39.1)	43 (33.3)	*P* > 0.05
Oral tests[b]				
Unstimulated whole salivary flow (≤ 1.5 mL in 15 minutes)	13 (61)	102 (55.1)	78 (60)	*P* > 0.05
Salivary sialography (score ≥ 1 according to Rubin e Holt)	12 (57.1)	110 (59.4)	88 (67.6)	*P* > 0.05
Labial salivary gland biopsy[c]				
Focus score ≥ 1	11 (52.3)	98 (63.6)	71 (64.5)	*P* > 0.05

[a] Ocular tests were performed in all patients.
[b] Oral tests were performed in all patients.
[c] Labial salivary gland biopsy was performed in 21, 154 and 110 patients with elderly, adult, and young onset of disease, respectively.

4. Discussion

Primary SS is a common autoimmune disorder of adults, especially of the middle-age women. Although pSS commonly appears in the fifth decade of life [4], our study, performed in a large cohort of patients, shows that an elderly onset of the disease ($\geq$ 65 years) is not rare (6% of our patients).

In this study, we confirmed and extended the observations made by other authors [13]: the clinical expression of primary SS in elderly-onset patients is quite similar to the disease in the remaining patients. Additionally, onset in the old age does not influence serological manifestations of pSS, although the prevalence of some immunological markers (especially anti-Ro auto-antibodies) shows a decreasing trend in the elderly-onset group. Moreover, an elderly onset is not associated with a lower positivity of sialography, ocular tests, or labial minor salivary gland biopsy.

We found that disease duration at the time of diagnosis was longer in the patients diagnosed before 40 than in those diagnosed after 40 and 65 years of age (13.8 vs 11.4 and 9.7 years respectively) indicating that the young patient population had a longer disease duration and thereby an increased probability of developing lymphoproliferative disorders.

In pSS, a disease characterized by a wide spectrum of clinical symptoms, there is frequently a long delay between clinical onset and diagnosis; in these cases, it is often arbitrary to establish a date for the disease onset, even by the patients themselves. In the recent years, increasing numbers of patients with early pSS have been referred to the Rheumatology Units in Europe due to the better knowledge of the disease either by general practitioners or by patients themselves, as well as because of the wide diffusion of some diagnostic tools, such as auto-antibodies.

In contrast with our study, Haga and Jonsson [14] found a significant influence of age on serological abnormalities in pSS, but not on disease manifestations. Although the explanation for this apparently age-related variability in the expression of the disease is still unclear, demographic factors and differences in genetic predisposition or responsiveness of an aging immune system may be implicated [12]. It has been suggested that older and younger patients with systemic autoimmune diseases may have different genetic determinants of disease and respond to different triggering mechanisms [18–21]. The slightly less exuberant expression of immunological features in the older onset patients with pSS may reflect the senescence of the immune system [22].

Although pSS is a typical disease of middle-age adults, clinicians should not ignore that this disease may not rarely be diagnosed also among elderly patients. Moreover, our study, carried out in a large series of patients with pSS, shows little effect of an older age at onset on the main clinical and immunological manifestations of such a disease.

5. Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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