Original article

Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome

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Keywords: *Sjögren's syndrome; prevalence; prognosis*

Background Primary Sjögren's syndrome (pSS) is one of the autoimmune diseases with high incidence. There were several clinical investigations in Caucasian but seldom in Chinese. The aim of this study was to compare the difference of clinical manifestations, immunological features and prognosis of pSS between Caucasian and Chinese pSS patients.

Methods Five hundred and seventy-three patients who fulfilled the 2002 international classification (criteria) for pSS from Peking Union Medical College Hospital between 1985 and 2006 were screened retrospectively and compared with other populations.

Results (1) The study consisted of 524 (91%) female and 49 (9%) male patients (female: male=10.7: 1). Mean age at the onset of the disease was (39.0±13.7) years and in 169 (29.5%) patients the disease onset occurred before the age of 30 years. The average duration from disease onset to pSS diagnosis was 48 months (range, 1–552 months). It had been shortened during the recent five years. (2) Dry mouth (84.5%) and dry eyes (70.0%) were the most common symptoms, significantly lower than foreign patients (P=0.000). Two hundred and seventy-two (47.5%) patients presented with rampant caries, 160 (27.9%) with parotidomegaly. The positivity of xerostomia, xerophthalmia and salivary gland biopsy were 91.9%, 94.8% and 90.7%, respectively. (3) Systemic involvement occurred in 91.4% patients. Compared with studies done outside China, higher prevalence of fever 41.0%, myositis 4.9%, pericardial effusion 14.8%, pulmonary involvement 42.3%, renal involvement 33.5%, thyroid involvement 32.7%, pancrease involvement 5.6% (P <0.01) and lower prevalence of fatigue, lymphadenectasis and Raynaud's phenomenon (P <0.01) were seen. (4) Risk factors of death include pulmonary artery hypertension, liver damage and interstitial lung disease.

Conclusions Chinese pSS differs significantly from the non-Chinese cases in terms of the age of onset, systemic involvement, autoantibodies and proportional mortality rate. Lung and liver damage were found to be the highest risk factors of the disease prognosis.

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Primary Sjögren's syndrome (pSS) is a common diffuse connective tissue disease mainly involving exocrine glands. The pathological mechanisms of the disease are mostly unclear, no diagnostic criteria are satisfying. There are at least 6 international diagnostic criteria, such as Fox criteria, European criteria and so on. However, none of them was approved by the World Health Organization, which suggested better diagnostic criteria should be established. The incidence rate of pSS in China is 0.33%–0.77%.[1] We had previously used Fox criteria to investigate 116 pSS patients. We found that the age of Chineses patients at the onset was earlier than that of the Caucasians. The prevalence of liver damage and Raynaud's phenomenon were less than that in the Caucasians studies. In this study we used the American-European Consensus Group (AECG) 2002 criteria to evaluate clinical manifestations, immunological characteristics and prognosis for 573 pSS patients and compared the clinical data among different studies to obtain in depth understanding of the Chinese pSS patients as well as to improve diagnosis and treatment of the disease.

METHODS

Patients

All the 573 patients in Beijing Union Medical College Hospital between January 1985 and January 2006, with

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Table 1. Demographic characteristics and clinical manifestations with exocrine glands involvement in different studies

Variables	This study	Zhao et al[3]	García-Carrasco et al[4]	Skopoulí et al[5]	Davidson et al[6]	Alamanos et al[7]	Ramos-Casals et al[8]	Theander et al[9]
n	573	116	400	261	74	422	336	286
Year	2006	1997	2002	2000	1999	2004	2004	2006
Country	Chinese	Chinese	Spanish	Greek	British	Greek	Spain	Sweden
Criteria	AECG2002	Fox	European	European	Fox	AECG2002	AECG2002	AECG2002
Female (% (*n*))	91.4 (524)	87.9 (102)	93.3 (373)	96.2 (251)	–	95.3 (402)	93.2 (313)	91.3 (261)
Average age of onset (years)	39.0	38.4	52.7*	–	–	55.4*	58.5*	57.0*
Average internal from onset to diagnosis (months)	48.0	51.6	74.9	48.0	–	–	–	–
Dry mouth (symptom) (% (*n*))	84.5 (484)	86.2 (100)	97.5 (390)*	92.0 (240)§	90.5 (67)	100 (422)*	–	–
Dry eyes (symptom) (% (*n*))	70.0 (401)	84.5 (98)	92.8 (371)*	95.4 (249)*	93.2 (69)*	94 (397)*	–	–
Parotidomegaly (% (*n*))	27.9 (160)	50.9 (59)	18.3 (73)†	52.9 (138)*	48.6 (36)*	26 (100)	19.3 (65)‖	–
Rampant caries (% (*n*))	47.5 (272)	47.4 (55)	–	–	–	–	–	–
Xerostomia (% (*n*))	91.9 (501/545)	–	94.6 (351/371)	–	63.5 (47)*	87.4 (360)‡	–	–
Xerophthalmia (% (*n*))	94.8 (494/521)	–	77.1 (253/328)*	–	55.4 (41)*	94.8 (400)	–	–
Salivary gland biopsy (% (*n*))	90.7 (303/334)	–	74.1 (169/228)*	–	47.3 (35)*	98.8 (417)*	–	88.9 (241/271)

*P=0.000; †P=0.001; ‡P=0.002; §P=0.003; ‖P=0.004, compared with this study.

diagnosis of pSS according to AECG 2002 classification criteria[2] were retrospectively analyzed.

Retrospective analysis

All the information of clinical manifestations, blood biochemical tests, ultrasound imaging and follow-up information was compared with our report (1997),[3] García-Carrasco (2002),[4] Skopouli (2000),[5] Davidson (1999),[6] Alamanos (2004),[7] Ramos-Casals (2004),[8] Theander (2006)[9] research group. All the information was collected from outpatient and inpatient medical records

Statistical analysis

For the description of quantitative data, the normal distribution groups were described as mean ± standard deviation, and the skew distribution groups were described by the median. Differences in quantitative variables were analyzed by *t* test, or Mann-Whitney *U* test while the variables cannot satisfy the normal distribution. χ^2 test was used to evaluate associations of qualitative variables in the different groups or adoption rate of description in statics of attributes. A value of P <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS11.5 for Windows (SPSS Inc., USA).

RESULTS

Demographic characteristic and clinical performances with exocrine glands involvement

Sixty (10.5%) of the 573 pSS patients were outpatients. The majority were females (524, 91.4%) with a male to female ratio of 1.0 to 10.7. The mean age of onset was (39.0±13.7) years old (ranging from 4.0 to 80.0 years old, ≤30.0 years old accounting for 29.5%), significantly lower than the mean age of overseas pSS patients ((52.7±0.9) years, P=0.000)). The average interval from onset to diagnosis, which was 57 months before 2002, has dropped 24 months after 2002 (including 2002), leading to the total average interval of 48 months (range 1 month to 552 months, P=0.002). Main clinical manifestations with exocrine glands involvement in this study and comparisons with other studies are presented in Table 1.

System involvement

A total of 524 cases (91.4%) with systemic damage are presented in Table 2.

Hematological system involvement

Two hundred and eighty-four cases (49.6%) had hematological abnormalities involved 120 cases (42.3%) of leucopenia and 71 cases (25.0%) of thrombocytopenia, and 93 cases (32.7%) reporting both. Three out of 60 patients who checked the related tests (5.0%) developed hemolytic anemia. In 137 patients who underwent bone marrow biopsy, 27 cases (19.7%) showed lower thrombopoietin while 7 cases showed lower hyperplasia (5.1%).

Respiratory system involvement

In the 522 pSS patients with CT scan, 221 cases (42.3%) developed pulmonary diseases. From illness onset to diagnosed with lung lesions, the average time is 48 months (range 0 to 384 months). The prevalence of interstitial lung disease (ILD, 116/522, 22.2%) was highest, while pulmonary hypertension (44/352, 12.5%), multiple bullae (46/522, 8.8%), pleural effusion (30/522, 5.7%), multiple nodules (28/522, 5.4%), enlarged mediastinal lymph nodes (3/522, 0.6%), mediastinal mass shadow (3/522, 0.6%) and paramediastinal emphysema (1/522, 0.1%) were also reported.

Cardiac involvement

In the 352 patients with ultrasonic cardiogram, pericardial effusion occurred in 52 (14.8%) patients examined by ultrasonic cardiography, included 41 (78.8%) with a small amount of effusion fluid and the other 11 (21.2%) with middle or large amount of fluid. Atrioventricular conduction block occurred in 20/453 (4.4%) patients.

Liver involvement

One hundred and eighty-eight cases (32.8%) with liver damage were found after an average of 24 months (range 0 to 504 months) of the onset. Elevated gamma-glutamyl transpeptidase (168, 29.3%), alaine transferase (146, 25.5%), alkaline phosphatase (137, 23.9%), total bilirubin (60, 10.5%)

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Table 2. Comparisons of system involvement in pSS patients in different studies

Variables	This study	Zhao et al[3]	García-Carrasco et al[4]	Skopouli et al[5]	Davidson et al[6]	Alamanos et al[7]	Ramos-Casals et al[8]	Theander et al[9]
n	573	116	400	261	74	442	336	286
Fever (% (*n*))	41.0 (235)	15.6 (18)	6.0 (24)*	16.9 (44)*	–	–	–	–
Fatigue (% (*n*))	27.7 (159)	–	–	36.4 (95)¶	86.5 (64)*	–	–	–
Swelling of lymph nodes (% (*n*))	7.7 (44)	19.8 (23)	7.0 (28)	31.8 (83)*	18.9 (14)†	6.6 (28)	6.8 (23)	–
Purpura (% (*n*))	13.4 (77)	25.0 (29)‡	–	11.1 (29)	–	4.7 (20)	–	11.9 (29/244)
Raynaud's phenomenon (% (*n*))	17.6 (101)	12.9 (15)	15.5 (62)	47.5 (124)*	62.2 (46)*	34.6 (146)	–	–
Articular (% (*n*))	47.8 (274)	46.6 (54)	36.8 (147)†	74.7 (195)*	85.1 (63)*	39.0 (165)	42.0 (120)	–
Myositis (% (*n*))	4.9 (28)	3.4 (4)	1.3 (5)‡	1.1 (3)‖	–	–	–	–
Hematological (% (*n*))	49.6 (284)	–	–	–	–	–	–	–
Pulmonary (% (*n*))	42.3 (221/522)	10.3 (12)*	9.3 (37)*	29.9 (78)†	–	2.6 (11)*	9.5 (32)*	–
Cardiac effusion (% (*n*))	14.8 (52/352)	1.7 (2)*	–	1.5 (4)*	–	–	–	–
Hepatic (% (*n*))	32.8 (188)	17.2 (20)†	–	–	–	–	–	–
Pancreatic (% (*n*))	5.6 (27/481)	2.6 (3)	1.0 (4)*	–	–	–	–	–
Renal (% (*n*))	33.5 (192)	36.2 (42)	6.3 (25)*	11.5 (30)*	–	–	–	–
Thyroid (% (*n*))	32.7 (74/226)	–	15.3 (61)*	–	16.2 (12)§	–	–	–
Neurologic (% (*n*))	11.9 (68)	12.1 (14)	8.3 (33)	2.3 (6)*	5.4 (4)	–	7.1 (24)	–

*P=0.000; †P=0.001; ‡P=0.002; §P=0.006; ‖P=0.009; ¶P=0.012, compared with this group.

were reported. Totally 146/481 cases (30.4%) with hepatosplenomegaly were revealed by ultrasonography.

Forty-two pSS patients were checked by liver biopsy: 26 with swelling of liver cells or pot-like necrosis, 13 with local fragmentary necrosis, 2 with community board inflammation, and 1 with nodular hyperplasia. In the portal area, 19 cases showed mild inflammatory infiltration, 7 cases had severe inflammatory infiltration, besides 3 cases had focal lymphocytic infiltration, 5 cases had small bile duct hyperplasia, 2 cases had small bile duct damage and 6 cases had fibrous tissue hyperplasia.

Pancreatic involvement

In the 482 cases with abdominal ultrasound scan, 27 (5.6%) pSS patients were identified with pancreatic lesions with manifestations of acute pancreatitis (8 cases), chronic pancreatitis (16 cases), pancreatic occupying lesion (3 cases). All the lesions disappeared after the treatment of hormone therapy plus immunosuppressive agents.

Renal involvement

Among the 192 (33.5%) patients with renal involvement, 126 (22.0%) patients were found with proteinuria counted by 24-hour urine protein (mean value of (0.5±0.1) g). Renal tubular acidosis (RTA, 96 cases, 16.7%), especially type I-RTA (88, 91.7% in RTA) was the primary renal complication, the median onset time of which was 9.5 months (range 0–300 months). The secondary complication was kidney stones and/or renal calcification (45/481, 9.4%). Renal dysfunction occurred in 41 cases (7.2%) while just 14 cases (14.6%) were defined subclinical diseases.

Sixty-four patients with pSS in the study were evaluated by renal biopsy. Pathology manifestations included interstitial nephritis (21 cases), interstitial nephritis combined with mesangial proliferative glomerulonephritis (9 cases), interstitial nephritis combined with membranous nephropathy (4 cases), interstitial nephritis combined with diffuse proliferative glomerulonephritis (2 cases), interstitial nephritis combined with diffuse proliferative glomerulonephritis (2 cases), interstitial nephritis combined with focal proliferative glomerulonephritis (1 case), mesangial proliferative glomerulonephritis (12 cases), membranous nephropathy (6 cases), focal proliferative glomerulonephritis kidney (3 cases), diffuse proliferative glomerulonephritis (2 cases), acute tubular necrosis (1 case) and thin basement membrane nephropathy (1 case). Routine immunofluorescence examination revealed positive in 27 cases (47.4% of 57 cases), including IgG-positive (23 cases), which diffuse granular depositions were mainly in capillary loops or mesangial zones; C3-positive (13 cases); C1q positive (11 cases). Nine cases were reported with lupus nephritis at least 3 years after the diagnosis of pSS (36–288 months).

Thyroid involvement

In the 226 cases, 74 (32.7%) patients were found to have thyroid disorders. Abnormal thyroid function was shown in 54/220 cases (24.5%), including hypothyroidism (42 cases, 1 case of which was pituitary hypothyroidism), hyperthyroidism (12 cases). Anti-thyroid antibody was positive in 57/110 cases (51.8%).

Immunological characteristics

Antibodies and immune parameters are presented in Table 3.

Initial symptom

The top five common initial symptoms were dry mouth and dry eyes (166, 29%), fever (70, 12.2%), joint swelling or arthralgias (66, 11.5%), paroxysmal paralysis (41, 7.2%) and parotidomegaly (38, 6.6%).

Coexistence of connective tissue diseases

Other connective tissue diseases occurred in 44 (7.7%) patients not less than 3 years after the diagnosis of pSS, including systemic lupus erythematosus (SLE) in 25 cases, rheumatoid arthritis in 12 cases, polymyositis/dermatomyositis in 5 cases, systemic sclerosis in 2 cases.

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Table 3. Immunologic characteristics in pSS patients in different studies

Variables	This study	Zhao et al[3]	García-Carrasco et al[4]	Skopouli et al[5]	Davidson et al[6]	Alamanos et al[7]	Ramos-Casals et al[8]	Theander et al[9]
n	573	116	400	261	74	442	336	286
Antibodies (% (*n*))								
ANA	83.9 (474/565)	45.7 (53)*	73.5 (288/392)*	85.4 (223)	31.1 (23)*	94.0 (397)	83.0 (279)	84.5 (240/286)
Anti-SSA	83.5 (474/568)	68.1 (78)*	39.7 (153/385)*	54.8 (143)*	23.0 (17)*	50.5 (203/402)*	–	–
Anti-SSB	40.7 (231/568)	33.6 (39)	26.5 (102/385)*	29.5 (77)‡	14.9 (11)*	40.0 (160/400)	–	–
RF	61.3 (292/476)	43.0 (50)*	37.6 (146/388)*	58.6 (153)	40.5 (30)†	–	35.4 (119)*	57.5 (157/273)
Anti-RNP	13.8 (78/566)	46.6 (54)*	1.3 (4/312)*	1.5 (4)*	2.7 (2)‖	–	–	–
ACA	22.2 (41/185)	–	–	–	1.4 (1)*	–	–	–
AMA	18.3 (65/355)	–	4.8 (14/294)*	–	6.8 (5)§	–	–	–
AMA-M2	14.4 (45/313)	–	–	–	–	–	–	–
SMA	11.0 (39/353)	–	34.8 (102/293)*	–	–	–	–	–
ANCA	9.4 (24/254)	–	5.8 (9/154)	–	–	–	–	–
ACL	7.3 (21/286)	–	–	–	45.9 (34)*	–	–	–
Immune parameters (% (*n*))	–	–	–	–	–	–	–	–
γ globulin ≥30%	43.6 (217/498)	60.3 (70)†	–	–	–	–	24.0 (81)*	–
IgG≥20.0 g/L	61.2 (330/539)	58.6 (68)	–	–	–	–	–	23.7 (68/286)*
IgA≥5.0 g/L	22.8 (121/531)	18.1 (21)	–	–	–	–	–	–
IgM≥3.0 g/L	16.6 (88/529)	8.6 (10)¶	–	–	–	–	–	–
Low CH50	37.1 (159/429)	–	11.6 (35/302)*	–	–	–	15.0 (51)*	–
Low C3	14.4 (62/431)	–	3.3 (10/303)*	1.5 (4)*	–	–	12.0 (39)	21.0 (60)
Low C4	16.5 (52/315)	–	7.6 (23/302)†	16.9 (44)	–	–	12.0 (39)	21.7 (62)

*P=0.000; †P=0.001; ‡P=0.002; §P=0.014; ‖P=0.007; ¶P=0.029, compared with this group.

Prognosis

Eighteen patients died in this group with the average age of death (58.3±3.1) years. The median time from the onset to death was 86 months. Table 4 shows that infections, particularly lung infections were the most common cause of death (12/18 cases). Prognostic risk factors of pSS included pulmonary hypertension (*OR*=6.4, 95% *CI*: 2.0–20.1), ILD (*OR*=3.2, 95% *CI* 1.2–8.6), liver dysfunction (*OR*=4.8, 95% *CI*: 1.7–13.6) and IgM ≥3.0 g/L (*OR*=5.5, 95% *CI*: 2.1–14.5).

Table 4. Cause of death in the patients of pSS

Cause of death	*n*
Infections	12
Lung infections	7
Infective shock	2
Abdominal infections	1
Purulent peritonitis	1
Sepsis	1
Liver cirrhosis	3
Hepatic failure	1
Myocardial infarction	1
Epidural hematoma	1

DISCUSSION

Despite different diagnostic criteria, the finding that pSS occurs mainly in the middle-aged women coincided with previous studies, but the onset age was 10 years younger and the age-span larger than that reported in the other races.[10] Potential patients might be easily ignored by doctors because of many non-specific symptoms of pSS. Therefore, there would be a longer interval from the onset of symptoms to clinical diagnosis. What is gratifying is that this study indicated that the interval had already been significantly shortened with the doctor and patients' increasing awareness of pSS.

Most common symptoms of pSS patients are dry mouth, dry eyes, but the patients in this study did not make such complaints as frequent as their overseas counterparts. Among those complained, however, the positive ratio in dental, ophthalmological related examinations was higher. A possible explanation may be a lower age of onset of pSS patients in China. Compared with the older patients, younger patients have lower ratio of dry mouth or dry eyes caused by endocrine glands atrophy.[11] In addition, patients seldom go for a doctor for the reason of dry eye or dry mouth. As a result, only one third of patients showed initial symptoms of dry mouth or dry eyes in this study. Therefore, those who are suspected of pSS without complaint of dry eye or dry mouth, should undertake ophthalmological and dental examinations (including salivary gland biopsy) to avoid delaying the diagnosis.

The proportion of pSS patients with systematic damage in this study was as high as 91.4%, for the majority of patients in this study were inpatients. It also was related to the application of advanced detective methods for diagnosing early organ damage. For instance, only 10% lung involvement in such cases was reported a decade ago,[3] while the number has risen to 42% after the use of high-resolution lung CT. Compared with overseas studies, patients in this group had higher prevalence of visceral involvement. The difference is not only due to different research sources, inclusion criteria and definition to organs involvement, but also related with different race, ethnic, genetic and environmental factors.

ILD was at the head of pulmonary lesions, which was consistent with other studies. The results of HRCT also accorded with another study between 2000 and 2007 validating further that the most common type in these ILDs was nonspecific interstitial pneumonia.[12]

The proportion of pericardial effusion was similar to foreign study.[13] Interestingly, middle or large amount of effusion fluid was detected from one-fifth of these

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patients probably due to their serious illness or the infections.

Liver damage in pSS patients has no special features not only in liver function tests but also in pathological aspect. Its pathological changes were consistent with other reports,[14,15] which showed chronic active hepatitis-like, biliary cirrhosis-like or non-specific changes.

This study proved that the corticosteroids therapy was generally valid for pancreatic involvement, however, some relapsing cases reported before may need other treatments such as rituximab.[16]

Renal damage in pSS is common. In clinical practice the prominent lesion is renal tubular acidosis type I, complicated with hypokalemic paralysis, kidney stones and/or renal calcification. Apart from SLE, most of pSS renal damages are renal interstitial lesions, and glomerular damages are relatively rare and mild. Immunofluorescence staining can be positive, and depositions are mostly IgG, without C3 or C1q. Further study of renal involvement in pSS patients in our hospital between 1993 and 2006 analyzed the relationship between low C4 level and glomerular injury.[17]

Thyroid involvement in patients with pSS has received more attention in recent years for their high prevalence. Such rate in other domestic reports was 37%,[18] similar to this group, higher than those reported in other regions. Reduced thyroid function was the most common founding. With the development of the disease, hyperthyroidism turns to hypothyroidism labeled by positive anti-thyroid antibodies. The recent research considered the lesions as the result of the infiltration of B lymphoid cells.[19] Thus, patients with hypothyroidism should be precautious of the possibility of pSS.

In accordance with the past studies, antinuclear antibodies are the most frequent autoantibodies in pSS. As for pSS specific antibodies anti-SSA antibodies, positive rates were respectively 83.5%, higher than other study groups. Notably, anti-centromere antibody (ACA) and anti-mitochondrial antibody (AMA) were detectable in this group with the positive rates of 22.2%, 18.3% respectively, significantly higher than those reported in White. CH50 in this study was predominately highest through all the studies. The cases of lower C3 patients were paralleled to the groups evaluated by the AECG2002, but not paralleled to the others.

The relationship of SS and other connective tissue diseases has recently been concerned by clinical rheumatologists.[20,21] The most common connective tissue disease with pSS is SLE. Statistical data concluded that SS merged with SLE is different from SLE and pSS.[22,23] In pSS-SLE patients, pulmonary, renal, skin, central nervous, system involvement, and serositis occurred more often than in patients with SS alone. Thyroiditis, autoantibodies to Ro/SS-A, La/SS-B and ds-DNA was more frequent in the SS-SLE group than in patients with SLE. Genetic background of the patients did not differ significantly. However, a study found that pSS-SLE patients in Peking Union Medical College Hospital was in line with pSS classification standards with typical eye and mouth symptoms, anti-SSA, SSB antibody high positive rate, similar to the pSS-only patients but not the SLE-only patients.[23] A report about the clinical profiles of other pSS-onset systemic sclerosis diseases announced that they are more similar to pSS but have better prognosis.[24]

PSS patients have a greater risk of developing malignancy, particularly lymphoproliferative malignancy such as lymphoma. Hematological tumors and solid tumors such as breast cancer, thymoma were also mentioned before.[25]

Admittedly, the patients of this study were mainly inpatients, which tend to have severe illness with large span of onset age. The limitation in sampling may have induced bias in the results. Hence, further studies which are needed to validate the conclusion.

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