Concise report

Frequent development of chronic obstructive pulmonary disease in primary SS—results of a longitudinal follow-up

Thomas Mandl¹, Sandra Diaz², Olle Ekberg², Roger Hesselstrand³, Eeva Piitulainen⁴, Per Wollmer⁵ and Elke Theander¹

Abstract

Objectives. To study the longitudinal development of pulmonary function in patients with primary SS (pSS) and its association with respiratory symptoms, pulmonary radiographic findings and clinical features of pSS.

Methods. Forty-one pSS patients, previously evaluated by pulmonary function tests (PFTs), were included in the study. The patients were studied at baseline and follow-up by PFT and at follow-up also by high-resolution CT scan of the lungs, the St George’s Respiratory Questionnaire and by inflammatory and serological tests. The PFT results were compared with previously studied population-based controls, standardizing results with regard to gender, age, height, weight and tobacco consumption.

Results. The mean follow-up time was 11 years. The pSS patients displayed signs of both obstructive and restrictive lung disease at baseline and at follow-up, and deteriorated in forced expiratory volume in 1 s (FEV₁), ratio of FEV₁ to vital capacity and in diffusing capacity for carbon monoxide during follow-up. Chronic obstructive pulmonary disease (COPD) was diagnosed in 37% of the pSS patients at follow-up. In pSS patients, respiratory symptoms and radiographic abnormalities were common, although with a poor association with PFT variables.

Conclusion. The pSS patients showed signs of both obstructive and restrictive pulmonary disease and COPD commonly developed during follow-up. Respiratory symptoms and radiographic abnormalities were common but poorly associated with PFT in pSS patients.

Key words: pulmonary function, primary Sjögren’s syndrome, follow-up study.

Introduction

Primary SS (pSS) is an autoimmune disease affecting exocrine glands and also frequently non-exocrine organs, including the lungs [1–5]. Although cross-sectional studies have evaluated pulmonary function in pSS patients [3, 5–7], only a few have followed pulmonary function longitudinally, all of which have used older classification criteria for pSS [7–10]. Since immunological mechanisms seem to be involved in the pathogenesis of pulmonary manifestations [1, 6–10] and the American–European Consensus Criteria (AECC) [11] only include pSS patients with some evidence of autoimmunity, an increased prevalence of pulmonary involvement could possibly be expected in pSS patients diagnosed according to the AECC. The aims of this study were (i) to investigate pulmonary function and its development in patients with pSS; and (ii) to study its associations with respiratory symptoms and clinical, radiographic, inflammatory and serological features of pSS.

Materials and methods

Patients

Eligible patients for inclusion in the study were female pSS patients, diagnosed according to the AECC [11], with a
maximum age of 80 years, from the Malmö Sjögren’s Syndrome Registry, who had previously been investigated with pulmonary function tests (PFTs). Sixty-five female patients had previously been investigated with PFT, mostly due to the reporting of respiratory symptoms, e.g. cough or dyspnoea, and were invited to the study, 24 of whom declined participation. Forty-one pSS patients were thus included [mean age 62 (range 25–80) years]. The mean follow-up time was 11.2 (range 2.1–26.2) years. Twenty-six were never smokers, 12 former smokers and 3 current smokers. Of former smokers, none had been smoking after baseline PFT. At baseline, the total lung capacity (TLC) and residual volume (RV) had not been assessed in one patient, the diffusion capacity for carbon monoxide (DLCO) in two patients and reversibility assessed in one patient, the diffusion capacity for carbon monoxide (TLC) and residual volume (RV) had not been smoking after baseline PFT. At baseline, the total lung capacity (TLC) and residual volume (RV) had not been assessed in one patient, the diffusion capacity for carbon monoxide (DLCO) in two patients and reversibility test was lacking in two patients with forced expiratory volume in 1 s (FEV1)/vital capacity (VC) (i.e. ratio of FEV1 to VC <0.70). At follow-up, two patients were not studied by reversibility test.

PFT controls

The PFT controls consisted of 186 population-based females attending a general health survey, of whom 100 were never smokers and 86 were current smokers [mean age 45 (range 20–70) years]. Based on these PFT results, expected values for PFT variables were calculated using a linear regression model into which age, height, weight and tobacco consumption were added as covariates [12].

Methods

The pSS patients at baseline had been investigated by PFT. At follow-up, patients were evaluated by PFT, but also by high-resolution CT (HRCT) scans of the lungs, evaluation of respiratory symptoms by the St George’s Respiratory Questionnaire (SGRQ) [13, 14], smoking habits by a structured questionnaire, disease activity and patient’s symptoms by the European League Against Rheumatism (EULAR) Sjögren’s Syndrome Disease Activity and Patient Reported Indices (ESSDAI and ESSPRI, respectively) [15–17] and by inflammatory and serological tests. The study was approved by the ethics committee at Lund University (LU 8-2009). All participants gave written informed consent according to the Declaration of Helsinki.

PFTs

The PFT included static and dynamic spirometry from which the VC, TLC, RV, FEV1, FEV1/VC and DLCO were assessed. FEV1 and VC were measured before and after 1.0 mg inhaled terbutaline [FEV1 after reversibility test (FEV1rev) and VC after reversibility test (VCrev)] and FEV1 reversibility was calculated. TLC and RV were measured with body plethysmography. Lung function tests, including calibration, were performed in accordance with European Respiratory Society guidelines [18]. PFT variables were expressed as absolute numbers and percentages of expected values [12]. Chronic obstructive pulmonary disease (COPD) was defined as FEV1rev/VCrev <0.70. In cases lacking reversibility tests, COPD was ruled out if FEV1/VC ≥0.70 and COPD was suspected if FEV1/VC <0.70. Clinically significant reversibility was defined as FEV1 reversibility ≥12% and ≥200 ml [19, 20]. Due to different follow-up times in different patients, the change in PFT variables per follow-up year in each patient was calculated and compared with expected changes.

HRCT

HRCT scans with sections of 0.75 mm thickness were performed. For radiation hygiene purposes, only 20 slices, 15 mm apart, were performed.

Questionnaires

The patients completed the SGRQ and the symptom, activity, impact and total scores were calculated. Scores range from 0 to 100 with a low-score indicating good health [13, 14]. Disease activity was assessed by the ESSDAI, including 12 domains. The ESSDAI total score was calculated by adding the domain scores [15, 16]. Patient-reported disease-related symptoms were evaluated by the ESSPRI, where patients score symptoms of sicca, pain, somatic and mental fatigue. An ESSPRI total score is calculated as the mean of the four symptom scores [17]. The patients also completed a structured questionnaire on smoking habits, including smoking status, years of smoking and the average daily tobacco consumption when smoking.

Laboratory and additional tests

The degree of inflammation was evaluated by assessing ESR and serum levels of IgG, C3 and C4. Moreover, sera were analysed for the presence of RF, ANA, anti-SSA and anti-SSB antibodies. Brain natriuretic peptide (BNP) was assessed to rule out concomitant congestive heart failure.

Statistics

For comparison of PFT values, the paired samples $t$-test was used. For discrete variables, the $\chi^2$-test, Fisher’s exact test and McNemar’s test were used. For correlations, Pearson’s correlation coefficient was calculated. Values were presented as mean (s.d.), percentages with pathological results and mean differences between baseline and follow-up. P-values <0.05 were considered statistically significant.

Results

PFTs

At baseline, pSS patients were found to have a decreased VC, TLC and FEV1 while the RV and FEV1/VC were increased in comparison with expected values. At follow-up, pSS patients were found to have a significantly decreased VC, TLC, FEV1, FEV1/VC and DLCO while the RV was increased in comparison with expected values. During follow-up, FEV1, FEV1/VC and DLCO decreased while TLC increased in pSS patients.
### Table 1: Comparison of PFT results in patients with pSS, at baseline and at follow-up

<table>
<thead>
<tr>
<th>PFT variables and COPD prevalence</th>
<th>Baseline, mean (s.d.)</th>
<th>Follow-up, mean (s.d.)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, % expected</td>
<td>88.0 (13.9)**</td>
<td>89.3 (14.4)**</td>
<td>1.35 (−1.32, 4.01)</td>
</tr>
<tr>
<td>VC, l</td>
<td>3.37 (0.61)</td>
<td>3.08 (0.65)</td>
<td></td>
</tr>
<tr>
<td>TLC, % expected</td>
<td>93.8 (12.8)**</td>
<td>96.6 (11.3)*</td>
<td>2.77 (0.06, 5.48)*</td>
</tr>
<tr>
<td>TLC, l</td>
<td>5.24 (0.72)</td>
<td>5.33 (0.68)</td>
<td></td>
</tr>
<tr>
<td>RV, % expected</td>
<td>111.6 (24.2)*</td>
<td>109.8 (19.4)**</td>
<td>−1.81 (−8.71, 5.09)</td>
</tr>
<tr>
<td>RV, l</td>
<td>1.90 (0.40)</td>
<td>2.21 (0.44)</td>
<td></td>
</tr>
<tr>
<td>FEV1, % expected</td>
<td>91.7 (16.2)**</td>
<td>84.5 (16.6)**</td>
<td>−7.16 (−10.57, −3.74)**</td>
</tr>
<tr>
<td>FEV1, l</td>
<td>2.70 (0.56)</td>
<td>2.21 (0.60)</td>
<td></td>
</tr>
<tr>
<td>FEV1/VC, % expected</td>
<td>103.8 (10.0)**</td>
<td>95.8 (12.0)*</td>
<td>−8.06 (−10.93, −5.18)**</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.800 (0.084)</td>
<td>0.716 (0.097)</td>
<td></td>
</tr>
<tr>
<td>DLCO, % expected</td>
<td>98.2 (22.1)</td>
<td>91.2 (18.0)**</td>
<td>−7.01 (−12.05, −1.96)**</td>
</tr>
<tr>
<td>DLCO, mmol/min kPa</td>
<td>7.50 (1.68)</td>
<td>6.15 (1.38)</td>
<td></td>
</tr>
<tr>
<td>COPD, %</td>
<td>7 (3/41)*</td>
<td>37 (15/41)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PFT results are presented as a percentage of expected and in absolute numbers [mean (s.d.)] and COPD diagnosis in percentage. In comparisons between PFT values, the paired samples t-test was used. The differences between PFT results at baseline and follow-up are presented as mean differences (95% CIs). In the comparison of COPD diagnosis between baseline and follow-up, the McNemar’s test was used. *Two of the three COPD patients had not been evaluated by reversibility test at baseline. **P < 0.05 vs expected values, ***P < 0.01 vs expected values, ****P < 0.001 vs expected values. *P < 0.05 vs baseline, **P < 0.01 vs baseline, ***P < 0.001 vs baseline.

Table 1). Furthermore, FEV1 and FEV1/VC were found to decrease and the TLC to increase significantly more per follow-up year in pSS patients in comparison with expected changes, while the changes in other PFT variables per follow-up year were not significant (Fig. 1).

At baseline, 7% (3/41) of pSS patients were diagnosed with definite or suspected COPD. At follow-up, 37% (15/41) of pSS patients fulfilled COPD criteria and 10% (4/39) had clinically significant reversibility, two of whom belonged to the COPD group. Nine had mild and six had moderate COPD [19]. COPD diagnosis was more common in ever-smoking (73%, 11/15) than in never-smoking pSS patients (15%, 4/26). The FEV1/VC was found to correlate inversely with the number of pack years (r = −0.457; P = 0.001) and smoking years (r = −0.439; P = 0.001).

**Radiographs**

In the HRCT scans, interstitial changes (often judged as mild), bronchiectasias, traction bronchiectasias, emphysema, ground glass opacities and honeycombing were found in 54, 44, 27, 15, 7 and 0%, respectively. Radiographic abnormalities and PFT variables were poorly correlated.

**SGRQ**

The SGRQ symptom, activity, impact and total scores were 29.0 (21.7), 45.3 (22.7), 16.6 (16.8) and 27.4 (17.0), respectively. PFT variables at follow-up and SGRQ scores were poorly correlated. However, the SGRQ activity, impact and total scores were found to correlate significantly with the ESSDAI and the ESSPRI total scores (data not shown).

**Clinical and laboratory variables**

At follow-up, one patient was chronically treated with inhaled CSs and four with inhaled bronchodilators, but none required oxygen therapy. In the ESSDAI respiratory domain, 54% had no activity, 27% low activity, 20% moderate activity and 0% high activity. The ESSDAI total score was found to inversely correlate with VC (r = −0.463; P = 0.002), FEV1 (r = −0.415; P = 0.007) and DLCO (r = −0.351; P = 0.025) at follow-up. If the respiratory domain was excluded from the ESSDAI, the correlations disappeared. The ESSPRI total score did not correlate with the PFT variables. PFT variables were poorly associated with ANA, RF, anti-SSA or anti-SSB antibodies, ESR, IgG, C3, C4, BNP, extraglandular disease and disease duration.

**Discussion**

In this study, pSS patients showed signs of mainly obstructive but also discrete restrictive pulmonary disease. COPD was diagnosed in 37% of the pSS patients at follow-up and was more prevalent among ever smokers. Respiratory symptoms and radiographic abnormalities were common in pSS patients, but were poorly associated with PFT variables.

Since the PFT variables were standardized with regard to age, height, weight and tobacco consumption, the findings of a decreased FEV1 and VC at baseline and at follow-up as well as a significant deterioration of the DLCO, FEV1 and FEV1/VC during follow-up imply that the disease itself may result in both obstructive and restrictive pulmonary disease, which is in line with previous reports.
The deteriorations of FEV₁ and FEV₁/VC during follow-up could imply that mucosal dryness in the airways and decreased mucociliary clearance may give rise to obstructive airway disease, although inflammatory mechanisms engaging exocrine glands in the airways may also be involved. The prevalence of COPD was unexpectedly high, even considering that ever smokers were five times more prone to be diagnosed with COPD at follow-up than never smokers. The high prevalence of COPD, especially in ever smokers, may be due to the selection of subclinical COPD patients among pSS patients when performing the PFT at baseline. Of note, however, was that only 7% (3/41) of the pSS patients were diagnosed with definite or suspected COPD at baseline, and none of the former smokers had smoked during follow-up. Another explanation could also be that disease-specific mechanisms, including sicca and smoking, may interact in the pathogenesis of COPD in these patients. In addition, the application of a fixed FEV₁/VC ratio may also lead to an overestimation of COPD, especially in elderly subjects. Nevertheless, these findings underline the importance of recommending that pSS patients with respiratory symptoms refrain from smoking.

In addition, pSS patients had a decreased DLCO at follow-up as well as a deterioration of DLCO during follow-up. The decreased DLCO has been previously reported in pSS patients [5, 7–10], although deterioration has only been reported in one [7], whereas other studies reported stabilization or improvement over time [8–10]. In the absence of radiographic signs of emphysema in most patients, the reduced DLCO could be due to discrete restrictive pulmonary disease, also in line with the decreased VC. Although the lack of association between radiographic interstitial changes and the DLCO is contradictory, the lack of association could imply that these often mild radiographic changes may be unspecific. Interstitial changes and bronchiectasias were both common findings in pSS patients, whereas ground glass opacities were only described in a few and honeycombing in none, in line with previous reports [1–3].

In our study, the SGRQ showed that respiratory symptoms were common in pSS patients. The SGRQ scores as well as several PFT variables correlated with the ESSDAI, which was not surprising considering that respiratory symptoms and PFT variables contribute to the score in its respiratory domain. The SGRQ scores, however,
were poorly associated with PFT, but correlated with the ESSPRI, which could be due to the SGRQ tapping other symptoms in pSS patients than intended, including symptoms of airway sicca, thereby explaining the poor correlation with PFT.

In previous studies, associations between anti-SSA antibodies [8, 9], focal sialoadenitis [8], hypergammaglobulinemia, β2-microglobulin [10] and PFT have been described. In contrast with previous reports, we could not demonstrate an association between any serological or immunological factors and PFT, possibly due to differences in patient selection.

The strengths of this study were the application of the AECC for pSS, the assessment of pulmonary dysfunction signs and symptoms with different modalities and the long-term follow-up. Limitations were selection of patients previously studied by PFT due to respiratory symptoms. Differences in follow-up time and disease duration between patients may have influenced the possibility of detecting non-linear changes of PFT variables. Furthermore, due to the lack of baseline HRCT scans of the lungs, and lacking clinical and PFT data during follow-up, the evolution of radiological changes over time and the influence of other co-morbidities on pulmonary function, e.g. respiratory tract infections, could not be assessed.

In conclusion, pSS patients showed signs of mainly obstructive but also discrete restrictive pulmonary disease that deteriorated during follow-up, and COPD indeed became a very common finding. Respiratory symptoms and radiological abnormalities were common in pSS patients but were poorly associated with PFT variables, as were inflammatory and serological features of pSS.

**Rheumatology key messages**

- The pSS patients showed signs of obstructive and restrictive pulmonary disease.
- COPD often developed in pSS patients.
- Pulmonary function was poorly associated with respiratory symptoms and radiographic abnormalities.

**Acknowledgements**

We thank study nurses Karina Palm and Britt-Marie Rylander for excellent support in the study.

**Funding**: The study was supported by grants from Malmö Rheumatism Association and the Swedish Rheumatism Association.

**Disclosure statement**: The authors have declared no conflicts of interest.

**References**


Clinical vignette

Whipple’s disease diagnosis following the use of TNF-α blockade

A 46-year-old man with inflammatory back pain and large and small joint arthritis was diagnosed with AS 10 years following symptom onset. Physical examination showed decreased vertebral range of motion. Laboratory revealed ESR of 40 mm/h, RF negative, ANA negative with positive HLA-B27. Plain radiographs demonstrated sacroiliac pseudo-widening. Anti-inflammatory, MTX (25 mg s.c. weekly) and prednisone (7.5–10 mg daily) were initiated. Five months later, infliximab (5 mg/kg increased to 10 mg/kg every 6 weeks) was added for inflammatory back pain with improvement.

After 2 years of infliximab, the patient developed fevers and migratory arthritis precipitating hospitalization. Abnormal laboratories included white blood cell (WBC) count 36 k/mm³, haemoglobin (Hgb) 11.6 g/dl and ESR 58 mm/h. Evaluation including WBC scan, histoplasma antigen, brucella serology, routine and lysis centrifugation blood cultures, hepatitis and HIV serology, and bone marrow biopsy were negative. Symptoms resolved with cessation of infliximab and MTX. Three months later, re-challenge with adalimumab and MTX for recurrent inflammatory symptoms resulted in fevers, migratory arthritis and new weight loss with diarrhoea. Endoscopy with duodenal biopsy showed altered architecture and intracellular bacilli on periodic acid–Schiff stain (Fig. 1). Tropheryma whipplei was detected from blood and duodenal tissue by PCR. Intravenous ceftriaxone (2 g daily for 2 weeks) was commenced followed by trimethoprim-sulphamethoxazole with improved symptoms.

Tropheryma whipplei is a ubiquitous organism, rarely associated with multisystemic and relapsing disease. The organism may be detectable by PAS staining of involved organ tissue or with 16S rRNA gene identification [1]. Arthropathies associated with T. whipplei may precede diagnosis and exhibit axial and peripheral involvement, with symptom exacerbation following TNF-α inhibitors [1, 2]. Our case illustrates the consideration of alternative aetiologies in patients with articular symptoms, most importantly following clinical deterioration on immunomodulatory agents like TNF-α inhibitors.

Disclosure statement: The authors have declared no conflicts of interest.

Jasmine R. Gaddy1,2, Zartash Z. Khan3,4, Brad Chaser5 and R. Hal Scofield2,6,7

1Department of Rheumatology, Immunology and Allergy, University of Oklahoma Health Sciences Center, 2Department of Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, 3Department of Infectious Diseases, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 4Infectious Disease Consultants, PA, Wichita, KS, 5Department of Pathology, University of Oklahoma Health Sciences Center, 6Department of Endocrinology and Diabetes, University of Oklahoma Health Sciences Center and 7Veterans Affairs Medical Center, Department of Endocrinology, Diabetes and Metabolism, Oklahoma City, OK, USA Correspondence to: Jasmine R. Gaddy E-mail: jasminegaddy@yahoo.com

References