Increased bronchial responsiveness in primary and secondary Sjögren's syndrome

A. Potena*, R. La Corte**, L.M. Fabbri⁺, A. Papi***, F. Trotta**, A. Ciaccia***

Increased bronchial responsiveness in primary and secondary Sjögren's syndrome. A. Potena, R. La Corte, L.M. Fabbri, A. Papi, F. Trotta, A. Ciaccia.
ABSTRACT: We examined one group of 33 patients with primary Sjögren's syndrome, one group of 17 patients with secondary Sjögren's syndrome, i.e. associated with other connective tissue diseases, and one group of 14 patients with connective tissue diseases but without Sjögren's syndrome. In each patient we obtained chest radiographs and measured lung volumes, carbon monoxide diffusing capacity and airway responsiveness to methacholine. We observed no difference in chest radiograph abnormalities, in lung volumes and in carbon monoxide diffusing capacity among the three groups. However, we found a slight but significant increase of bronchial responsiveness in patients with primary and secondary Sjögren's syndrome compared with patients with connective tissue disorders but without Sjögren's syndrome. Thus $PD_{20}FEV_1$ methacholine was 1.07 mg (1.2) (geometric mean and GSEM) in primary Sjögren's syndrome, 0.91 mg (1.4) in secondary Sjögren's syndrome (NS), and 2.24 mg (1.09) in patients with connective tissue diseases but without Sjögren's syndrome (t=2.59 and t=2.8, both p<0.05, vs primary and secondary Sjögren's syndrome, respectively). These results show that some patients with Sjögren's syndrome have mild bronchial hyperresponsiveness, which may be related to the specific airway abnormalities of this disease.
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Depts of * Medicine and ** Rheumathology, S. Anna Hospital, USL 31, Ferrara, *** Institute of Pulmonary Diseases, University of Ferrara, affiliated to ⁺ The Interuniversity Center on "Cellular and Molecular Mechanisms of Lung Injury".

Correspondence: Dott. A. Potena, Servizio di Fisiopatologia Respiratoria, Prima Divisione di Medicina, Arcispedale Sant' Anna, USL 31, Ferrara, Italy.

Sjögren's syndrome is a chronic inflammatory disease characterized by lymphoid infiltration of salivary and lacrimal glands which reduces their function and causes xerostomia and keratoconjunctivitis sicca [1]. Pulmonary involvement has been reported both in primary [2–4] and secondary (i.e associated with other connective tissue autoimmune diseases) [5–7] Sjögren's syndrome, but the prevalence and characteristics of the pulmonary function changes are still uncertain.

Lymphocytic infiltration of the submucosal glands as well as of the bronchial mucosa is present in patients with both primary or secondary Sjögren's syndrome and pulmonary involvement, suggesting chronic airway inflammation [1–7]. Airway inflammation is an important determinant of airway hyperresponsiveness in asthma [8] and lymphocyte infiltration of the airway mucosa is present in asthmatic subjects [9]. We speculated that chronic inflammation of the airways present in some subjects with primary or secondary Sjögren's syndrome or connective tissue disease could cause an increase of bronchial responsiveness.

The numerous glands and secretory cells make the airways a preferential target of lymphocytes in Sjögren's syndrome, because the pathogenesis of the disease is supposed to be related to an autoimmune reaction against exocrine gland components. Damage to the gland and the inflammatory cells might affect the characteristics of airway secretions and, thus, modify mucociliary clearance [10] and the composition of the fluid lining the airways [11, 12]. Changes of osmolarity may be involved in exercise-induced bronchoconstriction [13] and the administration of hyperosmolar aerosolized solutions may increase airway responsiveness [14].

Because Sjögren's syndrome is associated with both airway inflammation and changes of secretions, we speculated that the disease could also be associated with airway hyperresponsiveness. Having observed that some patients affected by Sjögren's syndrome had bronchial hyperresponsiveness, we wondered whether bronchial hyperresponsiveness was associated with the "sicca" syndrome or with the autoimmune inflammatory systemic disease. To address this question, we separated the subjects with primary and secondary Sjögren's syndrome and compared them with subjects with connective tissue diseases not associated with Sjögren's syndrome.

Subjects and methods

We examined 64 patients who were recruited sequentially, and divided them into three groups:
1. Thirty three subjects with primary Sjögren's syndrome.
2. Seventeen subjects with secondary Sjögren's syndrome,

associated with rheumatoid arthritis (n=6), systemic lupus erythematosus (n=3), progressive systemic sclerosis (n=5), mixed connective tissue disease (n=2) and polymyositis (n=1).

3. Fourteen subjects with connective tissue disorder (8 with progressive systemic sclerosis, 4 with rheumatoid arthritis, 1 with systemic lupus erythematosus and 1 with mixed connective tissue diseases).

lupus erythematosus, systemic sclerosis and mixed connective tissue diseases were diagnosed according to the American Rheumatism Association's (ARA's) criteria [17–19]. Primary or secondary Sjögren's syndrome was considered to be present when patients had clinical symptoms and laboratory evidence of keratoconjunctivitis, xerophthalmia, xerostomia and positive salivary gland lip biopsy, i.e. a local lymphocytic infiltrate <1

Table 1. – Anthropometric and clinical characteristics of the subjects examined

	Primary Sjögren's syndrome	Secondary Sjögren's syndrome	Connective tissue disease
Age yrs	51±15	52±14	55±11
Height cm	161.5±6.5	162.3±6.3	160.6±8.3
Smokers	5/33	3/17	1/14
Duration of disease yrs	4.1±4.2	6.4±7.7	9.1±9.3
Positive Schirmer's	100%	100%	0%
Positive lip biopsy	100%	100%	0%
Positive ANA test	20/33	13/17	8/14
Mean IgG mg·dl^{-1}	1919±891	1669±660	1367±250
Mean IgA mg·dl^{-1}	286±120	264±105	265±160
Mean IgM mg·dl^{-1}	178±84	198±100	151±89

Ig: immunoglobulin: ANA: antinuclear antibody.

The characteristics of the subjects are reported in table 1. No patient had been treated with steroids in the two months preceding the study and most of the patients were studied at the time that the diagnosis was first established. The diagnosis of Sjögren's syndrome was based on the contemporary presence of keratoconjunctivitis sicca and xerostomia. Three criteria were used for the presence of keratoconjunctivitis sicca: 1) positive answers to an appropriately designed questionnaire [15]; 2) wetting of 5 mm or less when the Schirmer test was performed with standard filter paper strips for 5 min [16]; and 3) anatomic abnormalities of the conjunctiva and the cornea. Three criteria were used for the presence of xerostomia: 1) positive answer to an appropriately designed questionnaire, 2) positive Saxon test (<2.7/2 min) [15]; and positive minor salivary gland lip biopsy according to TARPLEY et al. [16]. Rheumatoid arthritis,

according to the classification of TARPLEY et al. [16]. Sjögren's syndrome was excluded in the patients of group 3 because of absence of symptoms, negative laboratory tests and absence of local lymphocytic infiltrate in the salivary gland biopsy.

All sera from the patients examined were analysed for antinuclear antibodies (ANA), rheumatoid factor (RF) antibodies to smooth muscle (SM), nuclear ribonucleoprotein (RNP), native deoxyribonucleic acid (DNA), and Sjögren's antigens (SS-A, SS-B) [19].

Quantitative determinations of immunoglobulin G (IgG), IgA and IgM were also performed on all patients. All sera were tested for antinuclear antibodies at four dilutions (1:20, 1:40, 1:80, 1:160) on four cryostat sections of mouse liver before testing. The findings were considered positive if the sera reacted to a titre of at least 1:40 [19–21].

All patients underwent clinical examination, chest radiographs, and respiratory function tests. Standard postero-anterior and lateral chest radiographs were analysed randomly and were subjectively evaluated blindly by two independent radiologists for the presence of reticulonodular interstitial density, pleural oppressions, interstitial fibrosis, alterations of the cardiac silhouette, and hypertransparence.

Lung function tests included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) curves and flow volume curves. Total lung capacity (TLC) was measured with the helium dilution technique [22], and single-breath carbon monoxide diffusing capacity (DLCO) with the single-breath method [23]. Pulmonary function tests were performed using the Transfer screen (Erich Jaeger, West Germany). Actual results of pulmonary function tests were expressed as percentage of predicted values [24].

Inhalation challenge with methacholine

Airway responsiveness to aerosolized methacholine was assessed in each subject according to the slightly modified protocol of CHAI et al. [25], as previously described in detail [26], using a MEFAR dosimeter (Ballini, Brescia, Italy) connected to a MEFAR jet nebulizer. The output of the nebulizer was 0.045±0.005 ml per five actuations, at an inlet pressure of 20 psi for 0.9 s. Eighty nine percent of the aerosol particles generated by this nebulizer have an aerodynamic mass median diameter of 0.5–4 μm [27].

After inhalation of the diluent, i.e. phosphate buffered saline, increasing, doubling doses of methacholine were administered at 5 min intervals, starting from 0.04 mg up to 2.56 mg. Ventilatory function was monitored by measurements of FEV_1. Baseline FEV_1 was taken as the best of two or three satisfactory spirometric tracings obtained 3 min after the beginning of a set of five inhalations of aerosolized phosphate buffered saline. Then FEV_1 was measured 3 min after the beginning of each set of five inhalations of increasing, doubling concentrations of aerosolized methacholine. Inhalations continued up to the maximum delivered dose, i.e. 2.56 mg, unless FEV_1 had fallen by more than 20% below baseline value.

To assess airway responsiveness, dose-response curves to methacholine were constructed by plotting the baseline value of FEV_1 and the best of two or three satisfactory tracings of FEV_1 obtained after each dose against the cumulative dose. The cumulative dose of methacholine producing a 20% fall of FEV_1 ($PD_{20}FEV_1$) was calculated by interpolation from the dose-response curve and was used as a measure of airway responsiveness.

The day to day variability of $PD_{20}FEV_1$ measured with this [27] or similar [28] methods is never greater than a doubling inhalation dose. Values above the cumulative delivered dose of 1.4 mg methacholine (obtained after a set of five inhalations of 16 mg·ml⁻¹) were considered to be normal, according to previous studies conducted by us [26] and to the normal values recommended by others with similar [29] or comparable [30] methods. In a previous study it has been reported that in a working population, more than 90% of the subjects have a

Table 2. – Respiratory function, chest radiograph findings, lung function and bronchial responsiveness to methacholine in the subjects examined

	Primary Sjögren's syndrome (PSS)	Secondary Sjögren's syndrome (SSS)	Connective tissue disease (CTD)
Cough	9/33a	3/17	0/14
Productive cough	4/33	1/17	0/14
Chest radiograph			
interstitial	1/33	2/17	0/14
reticulonodular	1/33	0/17	0/14
hypertransparence	3/33	1/17	2/14
TLC % pred	110±10	116±18	113±17
FEV_1 % pred	104±13	102±15	108±12
DLcosb % pred	94±18	89±20	112±43
Mean $PD_{20}FEV_1$ methacholine mg	1.1 (1.2)	0.9 (1.3)	2.2 (1.1)*
Methacholine responders	18/33 (62%)	8/17 (46%)	2/14 (14%)b

a: Chi-squared PSS vs CTD = 4.72, p<0.05; b: Chi-squared overall = 6.58, p<0.05; *: PSS vs CTD = 6.52, p<0.05; SSS vs CTD = 3.77, p<0.05. TLC: total lung capacity; FEV_1: forced expiratory volume in one second; DLcosb: single-breath diffusing capacity of the lungs for carbon monoxide; $PD_{20}FEV_1$: provocative dose producing a 20% fall in FEV_1.

$PD_{20}FEV_1$ above 160 cumulative Units, equivalent to a cumulative delivered dose of 1.42 mg methacholine [31].

Statistical analysis

All values are presented as mean±SEM with the exception of mean values of methacholine provocative doses which are reported as geometric means and geometric standard errors of the mean (GSEM). Statistical comparisons were made with the Student's two tailed t-test for unpaired data and the Chi-squared test for contingency tables. A level of >95% probability was considered to be significant.

Results

The anthropometric and clinical characteristics of the three groups of patients examined are reported in tables 1 and 2. Respiratory symptoms, lung function tests and chest radiographic findings were no different in the three groups of subjects examined, with the exception of cough that was significantly more frequent in patients with primary Sjögren's syndrome when compared with patients with connective tissue diseases (table 2, p<0.05). On average, pulmonary function tests were normal. However, patients with primary Sjögren's syndrome and secondary Sjögren's syndrome had bronchial hyper-responsiveness. $PD_{20}FEV_1$ was 1.1 (GSEM 1.2) in patients with primary Sjögren's syndrome, 0.9 (GSEM 1.3) in patients with secondary Sjögren's syndrome, and 2.2 (GSEM 1.1) (t=2.59 and t=2.80, both p<0.05, vs primary and secondary Sjögren's syndrome) in patients with progressive connective tissue diseases (table 2 and fig. 1).

The number of subjects with increased airway responsiveness, i.e. with a $PD_{20}FEV_1$ <1.4 mg, was 18 out of 33 in the group of patients with primary Sjögren's syndrome, 8 out of 17 in the group of patients with secondary Sjögren's syndrome and 2 out of 14 in the group of subjects with connective tissue disease not associated with Sjögren's syndrome (p<0.05) (table 2).

The degree of airway responsiveness was not correlated with the severity or the duration of the disease, with the degree of lymphocytic infiltration of the salivary glands or with symptoms, lung function, or immunological laboratory test. Lung function tests and chest radiograph findings were no different in hyperreactive subjects as compared to nonhyperreactive subjects.

Discussion

This paper shows that primary and secondary Sjögren's syndrome, but not connective tissue disorders, are associated with a slight increase of bronchial responsiveness to methacholine. Even though we cannot exclude a selection bias, because the patients were not randomly selected, such selection bias is unlikely because none of the invited patients refused to perform the methacholine inhalation challenge.

Previous studies demonstrated a variable involvement of the pulmonary system in Sjögren's syndrome. Rhinitis sicca, persistent hoarseness, chronic dry cough in addition to increased incidence of respiratory tract infections have been attributed to bronchial gland atrophy and "lymphocytic" bronchitis [28–30]. The number of subjects with interstitial pulmonary fibrosis
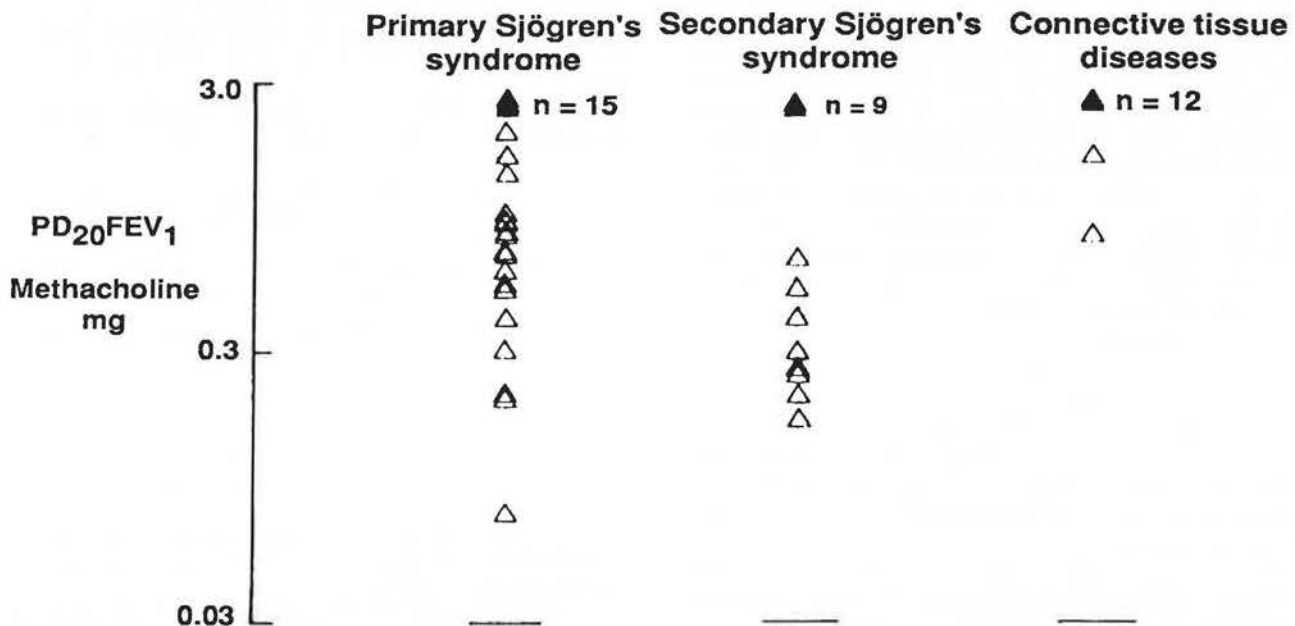

Fig. 1. – Bronchial responsiveness to methacholine in the subjects examined. $PD_{20}FEV_1$: provocative dose of methacholine producing a 20% fall in forced expiratory volume in one second.

on the chest radiographs was no different in the three groups examined in this study, nor was the lung function or the prevalence of respiratory symptoms different (table 3).

Cough was present only in subjects with primary or secondary Sjögren's syndrome. Bronchial hyperresponsiveness was present in six of the nine subjects with primary and in two of the three subjects with secondary Sjögren's syndrome who complained of cough. However, bronchial hyperresponsiveness was also present in seven of the 24 subjects with primary and four of the 14 subjects with secondary Sjögren's syndrome who did not complain of cough. Although we did not assess the severity of cough, which might indeed be related to the degree of bronchial hyperresponsiveness, these data suggest that bronchial hyperresponsiveness may not be strictly related to cough. Dry cough may precede the development of Sjögren's syndrome by many years. Thus, previous studies have suggested that in the presence of dry cough the potential development of Sjögren syndrome should be considered in the diagnostic procedure [2, 32, 33]. Our results suggest that airway hyperresponsiveness should also be considered as a sign of bronchopulmonary involvement in the Sjögren's syndrome.

The results of the present study suggest that the pathogenesis of bronchial hyperresponsiveness observed in patients with Sjögren's syndrome is probably related more to specific exocrine gland alterations than to the systemic autoimmune disease, because bronchial responsiveness was not present in patients with connective tissue disease but not Sjögren's syndrome.

As the lymphocytic infiltration of the glands seems to be the cause of the changes of secretions, it might be difficult to identify the relative importance of the two features of the disease, i.e. lymphocytic infiltration and altered fluid composition, on the pathogenesis of bronchial hyperresponsiveness. Unfortunately, there are no data on the characteristics of the fluid lining the airways in subjects with Sjögren's syndrome. However, tears [34] and saliva [35] are indeed hyperosmolar and, thus, the airway fluid may also have altered composition of ions and macromolecules. Further studies are required to investigate the pathological changes and the characteristics of secretions associated with airway hyperresponsiveness in Sjögren's syndrome. There is increasing evidence that lymphocytic infiltration of the airways mucosa may be associated with bronchial hyperresponsiveness in stable asthma, but there is so far no evidence of a cause-effect relationship [9, 36]. Hyperosmolar solutions cause bronchoconstriction and increase airway responsiveness in asthmatic subjects [13–14, 37, 38] but there is no experimental evidence that the fluid lining the airways is hyperosmolar at hyperosmolarity of that fluid is the cause of bronchoconstriction and/or hyperresponsiveness.

In conclusion, the present paper shows that some subjects with primary and secondary Sjögren's syndrome complain of cough and/or have a slight increase of bronchial responsiveness, suggesting that airway involvement may be significant in this disease.

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Augmentation de la réactivité bronchique dans le syndrome de Sjögren primaire et secondaire. A. Potena, R. La Corte, L.M. Fabbri, A. Papi, F. Trotta, A. Ciaccia.

RÉSUMÉ: Nous avons examiné un groupe de 33 patients atteints d'une syndrome de Sjögren primaire, un groupe de 17 patients atteints d'un syndrome de Sjögren secondaire (c'est-à-dire associé à d'autres maladies du tissu conjonctif), et un groupe de 14 patients avec des conjontivites mais sans syndrome de Sjögren. Pour chaque patient, nous avon obtenu des clichés thoraciques et mesuré les volumes pulmonaires, la capacité de diffusion du CO, et la réactivité des voies aériennes à la methacholine. Nous n'avons pas observé de différence dans les anomalies des clichés thoraciques, des volumes pulmonaires, de la capacité de diffusion, entre les trois groupes. Toutefois, nous avons observé une augmentation légère mais significative de la réactivité bronchique des patients atteints de syndrome de Sjögren primaire ou secondaire, par comparaison avec ceux atteints de conjonctivite mais sans syndrome de Sjögren. Donc, la $PD_{20}FEV_1$ methacholine était de 1.07 mg (1.2) (moyenne géométrique et erreur standard de la moyenne) dans le syndrome de Sjögren primaire, de 0.91 mg (1.4) dans le syndrome de Sjögren secondaire (NS) et de 2.24 mg (1.09) chez les patients atteints de conjonctivite sans syndrome de Sjögren (t=2.59 et t=2.8, pour tous deux p<0.05, par rapport au syndrome de Sjögren respectivement primaire et secondaire). Ces résultats montrent que certains patients ayant un syndrome de Sjögren développent une légère hyperréactivité bronchique qui peut être en relation avec les anomalies spécifiques des voies aériennes dans cette maladie.
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