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Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study

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Summary
The etiology of idiopathic pulmonary fibrosis (IPF) remains poorly understood, but some studies have suggested that cigarette smoking or other occupational or environmental exposures, diabetes mellitus, or gastroesophageal reflux may play a role. In this study we evaluated the clinical records of a group of 97 consecutive patients with IPF, and 560 patients suffering 5 different respiratory disorders that were examined as controls: asthma ($n = 111$), chronic obstructive pulmonary disease ($n = 132$), squamous cell lung carcinoma ($n = 118$), lung adenocarcinoma ($n = 101$) and patients with otorhinolaryngology problems but without lung disease ($n = 98$). In bivariate analyses male sex, diabetes mellitus and being former cigarette smoker were associated with IPF. After adjusting by these variables, multivariate analysis revealed that type 2 diabetes mellitus [11.3% in IPF patients vs 2.9% in controls, OR = 4.3 (95% CI: 1.9–9.8), $p < 0.0001$] was an independent risk factor associated to IPF. Our results provide additional evidence of a putative relationship between DM2 and idiopathic pulmonary fibrosis. Experimental research is necessary for thorough assessment of the pathogenic mechanisms involved in this association.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive scarring lung disease that leads to respiratory failure and death.[1] Although the etiology of IPF is still unknown, it is considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, up to now putative genes and environmental factors that consistently increase the risk of IPF have not been identified. Smoking presents the most

Abbreviations: COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; DM2, type 2 diabetes mellitus; ORL, patients with otorhinolaryngologic problems; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society.

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striking association with both the sporadic and the familial forms of IPF.[2,3] Likewise, some occupational and environmental exposures, primarily to wood and metal dusts, have shown to be associated to increased risk of IPF.[2] Chronic viral infection (Epstein-Barr virus) and gastroesophageal reflux have been also considered as possible risk factors for this disease.[4,5] The incidence of IPF increases with age, and aging contributes to some lifestyle-related diseases. Therefore, it is possible that lifestyle-related disorders such as type 2 diabetes mellitus (DM2) may affect either the initiation or progression of IPF. Actually, in two studies performed in different ethnic populations DM2 was found to be associated with IPF.[6,7]

In this context, the aim of the present study was to identify possible risk factors associated to IPF in a Mexican population. Our results indicated that DM2 is a major predictor of the disease.

Patients and methods

This was a retrospective case-control, hospital-based study performed at the National Institute of Respiratory Diseases (INER), México. Clinical records of consecutive IPF patients seen at this institute from 2000 through 2005 were reviewed. Diagnosis of IPF was made according to established criteria, and confirmed by lung biopsy in 35% of subjects.[8]

The control group was integrated by patients who were seen as outpatients or were hospitalized at the INER due to selected pulmonary diseases [asthma ($n = 111$), chronic obstructive pulmonary disease (COPD, $n = 132$), squamous cell lung carcinoma ($n = 118$), or lung adenocarcinoma ($n = 100$)] and by patients with otorhinolaryngologic (ORL, $n = 98$) problems but without lung disease. Diagnosis of asthma or COPD were done according to the Global Initiative for Asthma [GINA[9]] and the Global Initiative for Chronic Obstructive Lung Disease [GOLD[10]], respectively. Both types of lung cancer were confirmed by histopathology. Regarding ORL patients, individuals included in the analysis were randomly selected from patients assisting to the ORL department during the study period. Cases and controls were evaluated simultaneously. To confirm specific diagnoses of cases and controls, the clinical records were examined twice through standardized methods. Diagnosis of DM2 was done if the patient had a fasting glucose level higher than 126 mg/dl (7 mmol/l) in the absence of corticosteroids treatment, or the accomplishment of one of the following criteria: a) the patient knew that he or she had DM2 diagnosed by a clinician; b) diagnosis of DM2 was done at INER during the first consult; c) the patient was taking oral drugs for DM2; d) the patient had used insulin. The protocol was accepted by the Bioethics and Science Committee of INER.

Environmental exposures

Information concerning environmental exposures was obtained from a standardized questionnaire dealing with risk factors for respiratory diseases. This questionnaire was systematically applied by the Social Work Department to any patient admitted to the INER from 1999 onward. The questionnaire was created and validated by one of the authors (RPP) and assesses the following risk factors: age, gender, DM2, smoking habit (current, former, ever); alcoholism (current, former, ever); occupational exposure to dusts, smoke or chemicals; location and characteristics of the home (rural or urban area, construction materials, number of windows and number of hours they remain open, number of individuals living with the patient, presence of children <5 years old, home nearness to a gas station, high-traffic roads, landfills, dairy or poultry farms, and manufacturing plants); home exposure to wood smoke, coal, side-stream tobacco smoke, birds, carpets, dampness and insecticides.

Statistical analysis

Categorical variables were analyzed through the chi-square test. Interval variables were expressed as mean and standard deviation and were compared by the Student's *t*-test. Odds ratios (OR) were calculated through unconditional

Table 1 Sociodemographic characteristics of cases and controls ($n = 657$).

	IPF cases ($n = 97$)	Controls ($n = 560$)	OR (95%CI)
Age (*years*)	62.6 ± 11.0	62.3 ± 12.2	1.002 (0.9—1.02)
Male sex	71/97 (73.2)	347/560 (62.0)	1.7 (1.03—2.7)
Type 2 diabetes	11/97 (11.3)	16/560 (2.9)	4.3 (1.95—9.7)
Past or current occupational exposure to dust	55/97 (56.7)	292/560 (52.1)	1.2 (0.8—1.9)
Past or current occupational exposure to smoke	64/97 (66.0)	388/560 (69.3)	0.9 (0.5—1.4)
Past or current occupational exposure to chemicals	28/97 (28.9)	120/560 (21.4)	1.5 (0.9—2.4)
Tobacco smoke exposure			
Non-smoker	53/97 (54.6)	320/560 (57.1)	0.9 (0.6—1.4)
Ever smoker	44/97 (45.4)	240/560 (42.9)	1.1 (0.7—1.7)
Former smoker	39/97 (40.2)	168/560 (30.0)	1.6 (1.006—2.5)
Current smoker	5/97 (5.2)	82/560 (14.6)	0.3 (0.1—0.8)
Past passive smoker	36/95 (37.9)	213/544 (39.2)	0.9 (0.6—1.5)
Current passive smoker	9/96 (9.4)	129/542 (23.8)	0.3 (0.2—0.7)
Past or current alcohol use	39/97 (40.2)	221/560 (39.3)	1.03 (0.7—1.6)

Data correspond to mean $\pm$ SD or to frequencies (%).