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Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis

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Summary
Idiopathic pulmonary fibrosis (IPF) is a lethal lung disorder of unknown etiology. The disease is likely the result of complex interactions between genetic and environmental factors. Evidence suggests that certain environmental factors, such as cigarette smoking and metal dust exposures, or comorbidities like gastroesophageal reflux, and type 2 diabetes mellitus (DM2) may increase risk to develop IPF. Substantial uncertainty remains, however, regarding these and other putative risk factors for IPF. In this study we performed a case–control analysis including 100 patients with IPF and 263 controls matched for age sex and place of residence. We used a structured questionnaire to identify potential risk factors for IPF, including environmental and occupational exposures as well as the relevance of family history of pulmonary fibrosis. The multivariate analysis revealed that family history of pulmonary fibrosis [OR = 6.1, CI95% 2.3–15.9; $p < 0.0001$] was strongly associated with increased risk of IPF. Actually, 20% of the cases reported a parent or sibling with pulmonary fibrosis. Gastroesophageal reflux [OR = 2.9, CI: 1.3–6.6; $p = 0.007$], former cigarette smoking [OR = 2.5, CI: 1.4–4.6, $p = 0.003$], and past or current occupational exposure to dusts, smokes, gases or chemicals [OR = 2.8, CI: 1.5–5.5; $p = 0.002$] were also associated with the disease. Despite being a significant risk factor on univariate analysis DM2 was not significant in multivariate analysis. These

Abbreviation: ATS, American Thoracic Society; 95% CI, 95% confidence intervals; DLD, Division of Lung Diseases; DM2, Type 2 diabetes mellitus; ECRHS, European Community Respiratory SurveyII; ERS, European Respiratory Society; IIP, Idiopathic interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; LHSQ, Lung Health Study Questionnaire; OR, Odds ratio; SD, Standard deviation; SF-12, Short Form survey-12; TSR, telomere repeat copy number to single gene copy number.

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findings indicate that family history of pulmonary fibrosis is a strong risk factor for IPF. Also, we confirmed that occupational exposures, gastroesophageal reflux and former smoking increase the risk for this disease.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and lethal lung disorder of unknown etiology. The disease occurs predominantly in older adults, although the mechanisms for the association of aging with IPF have not been elucidated.[1] IPF is considered a complex disease where both genetic and environmental factors are believed to contribute to disease susceptibility. In the last decade a number of studies have tried to understand the genetic bases of this disease and to identify risk factors, but there are few large studies with conclusive results.

To date, smoking has consistently been associated with IPF in a number of case—control studies evaluating sporadic IPF and in one study of familial pulmonary fibrosis.[2,3] Also, several occupational factors, adjusted for age and smoking have been found significantly associated with IPF, including metal and wood dust exposure.[4,5] A meta-analysis supported that significant increased risk for IPF is associated with cigarette smoking and exposures to agriculture and farming, livestock, wood and metal dust, and stone and silica.[2] Likewise, some studies provide evidence of an association between IPF and type 2 diabetes mellitus (DM2) and gastroesophageal reflux.[6—10]

Familial IPF, which is virtually indistinguishable from sporadic IPF, is identified when two or more members of a family have the disease. Some studies suggest that 0.5—3.7% of IPF is familial.[11,12] However, a remarkably higher frequency was reported in a small cohort of IPF patients from a lung transplant program where 19% had a positive family history[13]; this retrospective decade-long analysis probably had higher detection due to subsequent cases occurring in the family of patients who reported a negative family history. More recently, 10% were identified as familial within a single-center cohort of 229 patients with idiopathic interstitial pneumonias.[14]

In this context, we designed a questionnaire-based, case—control study to identify potential environmental risk factors in our population as well as the relevance of family history of pulmonary fibrosis in a cohort of IPF patients.

Methods

Study design

A case—control study was carried out at the National Institute of Respiratory Diseases during 2007—2009. The research protocol was approved by the institutional Scientific and Bioethics Committee (*Comité de Ciencia y Bioética en Investigación; Protocol #E05-07*). Population studied was comprised of newly-diagnosed IPF patients (cases) consecutively seen at our institution, and healthy subjects (controls) paired by age, gender and residential area. Diagnosis of IPF was established according to ATS/ERS criteria.[15] In 35% of the patients the diagnosis was confirmed by surgical biopsy showing changes of usual interstitial pneumonia.[16] Healthy controls were randomly selected from the same patients' neighborhoods, at a ratio of 1—3 controls per IPF patient. In general, matching controls were living in houses located in the same block than the patients. A trained interviewer visited every household and asked if some person living there had the same age and gender than the case patient. After explaining the purpose of the study, potential control subjects were asked to participate and, if agreed, the questionnaire was applied. Control subjects were included in the study if they were no relatives of the patients and if they denied chronic pulmonary diseases or acute respiratory symptoms in the last three weeks prior to the interview. Patients and controls were individuals with the same ethnic origin and with at least two generations born in Mexico. Patients and controls have similar access and utilization to the same quality health care. A signed consent letter was obtained from all patients and controls.

Exposure assessment

Evaluation of exposures was performed with the same questionnaire used in the PLATINO study,[17,18] which in turn derives from an already validated questionnaire (ATS-DLD-78, ECRHS, LHSQ, SF-12). The PLATINO survey was enlarged by adding questions about chronic respiratory conditions in interviewed subjects' relatives. This questionnaire was applied to all cases and controls by two trained interviewers. Among other variables, characteristics of personal (tobacco, alcohol), occupational (dusts, smokes, gases, chemicals, dairy and poultry farms), and household (ventilation, wood smoke, tobacco smoke) exposures were investigated. The questionnaire also explores the presence of current or past presence of medical conditions such as gastroesophageal reflux, gastritis, hepatitis, heart diseases, and depression. Finally, chronic pulmonary diseases in parents and siblings were also assessed. This last question included the following specific diagnoses: chronic obstructive pulmonary disease, emphysema, asthma, lung cancer, tuberculosis and pulmonary fibrosis. A diagnosis of diabetes mellitus type 2 (DM2) was established through the questionnaire, evaluating whether it was diagnosed by a physician, type of medication (oral hypoglycemic agents or insulin), and duration. Additionally, in IPF patients, diagnosis of DM2 was confirmed by pre-prandial glucose $>$126 mg/dl without previous corticosteroid use.

Statistical analysis

Statistical analysis included Student's *t*-test and chi square test to evaluate differences between interval and categorical variables, respectively. Association between two variables was assessed through odds ratio (OR) and 95% confidence intervals (95%CI). Finally, multivariate models were generated by means of conditional logistic regression for matched case—control groups and included the variables that were confounders as those that were considered to be indispensable in explaining the study event. In this analysis, the following predictive variables were included: having a parent/sibling with pulmonary fibrosis, being a former cigarette smoker, past or current occupational exposure to dusts, smokes, gases or chemicals, past gastroesophageal reflux history, and DM2. Probability criteria for a variable entering to or removing from the model were 0.05 and 0.10, respectively. The analysis was performed using Stata software, Release 9.0.

Results

From January 2007 through December 2009 a total of 100 IPF patients and 263 healthy controls paired by age, gender and geographical region were studied. Average age was 67.8 ± 9.5 years (mean ± SD) in IPF patients and 67.9 ± 9.1 years in the control subjects ($p = 0.9$). Male predominance was comparable among cases and controls (71.0% versus 69.9%, respectively, $p = 0.8$). The similar age and gender between the cases and controls indicate that matching was successful. The majority of the study population (75.2%) lived in the residential areas of the two nearest political demarcations, *Distrito Federal* and *Estado de Mexico*.

Educational characteristics and tobacco smoke and other exposures of the study subjects are shown in Table 1. In the bivariate analysis, the IPF group had a marginal but significantly higher proportion of individuals with 6 or more education years [44.0 vs 32.3% from controls, OR = 1.6 (95% CI, 1.02—2.6), $p = 0.039$]. Occupational exposure to dusts, smokes, gases or chemicals was more frequently found among cases than in controls [77.0 vs 58.6%, respectively, OR = 2.4 (95% CI, 1.4—4.0), $p = 0.001$]. Regarding tobacco smoke exposure, former cigarette smokers also showed significant excess risk for IPF [58.0% vs 33.5%, OR = 2.7 (95% CI, 1.7—4.4), $p < 0.0001$].

As shown in Table 2, significantly more IPF patients answered affirmatively to the question about the presence of pulmonary fibrosis in a parent (father or mother) or sibling (brother or sister) [20.0% vs 2.7%, OR = 9.1 (95% CI 3.7—22.4), $p < 0.0001$]. Three of the 20 patients reported two relatives with the disease. We were able to corroborate the diagnosis of pulmonary fibrosis in the relatives of 8 of these 20 patients because the remaining 12 parents or siblings had died several years ago when we contacted the families. Diagnosis of pulmonary fibrosis in the 7 of the 8 familial cases was corroborated in our Institute using HRCT and pulmonary function tests. The last familial case was evaluated in another Hospital and diagnosis included HRCT and lung biopsy. However, even if we consider only these 8 patients, the odds ratio continued to be significantly increased [OR: 2.8 (95% CI 1.01—7.9), $p < 0.05$]. On the other hand, due to the potential existence of a recall bias (with IPF cases more prone to recall pulmonary disease in their relatives), we estimated the impact of a misdiagnosis among control group's relatives. Thus, cases and control subjects declared that 6 and 29 relatives, respectively, had chronic bronchitis, pulmonary emphysema, or chronic obstructive pulmonary disease. In this context, even if we consider that the 23 exceeding relatives of control subjects were in fact IPF patients, familial pulmonary fibrosis would remain significantly associated to IPF (20/100 and 30/263 in cases and controls, respectively) with OR: 1.9 (95% CI 1.04—3.6), $p = 0.04$.

As previously suggested in several studies on familial IPF,[11,12,14] our IPF patients with family history of pulmonary fibrosis were significantly younger than those with negative family history (61.8 ± 7.1 versus 69.3 ± 9.4 years old, $p < 0.001$). No other variable reached a significant difference between these two subgroups of IPF patients.

Some diseases were more often observed in IPF patients, as compared with controls. Significant increased risk for IPF was associated with past gastroesophageal reflux [OR = 3.1 (95% CI, 1.7—5.9) $p < 0.0001$], and gastritis [OR = 1.9 (95% CI 1.2—3.2) $p = 0.006$]. Type 2 diabetes mellitus was also more frequent among cases than controls [30.0 vs 19.0%, OR = 1.8 (95% CI, 1.1—3.1), $p = 0.02$]. Past or current cardiac disease was marginally associated with IPF (Table 2).

Concerning household characteristics, the only feature that was more frequently seen among cases was the presence of earthen floor [9.0 vs 3.4%, respectively, OR = 2.8 (95% CI, 1.1—7.2), $p = 0.035$]. Some other variables such as working in crop cultivation or as a stockbreeder, carpenter or hairdresser, household nearness to a dairy farm, birds at home, dampness at home, and indoor use of insecticides were not different between cases and controls (data not shown).

In the multivariate analysis, having a parent or sibling with pulmonary fibrosis was the strongest variable

Table 1 Education and exposures of cases and controls.

Characteristic	IPF cases[a] ($n = 100$)	Control subjects[a] ($n = 263$)	OR (CI95%)
Formal education ≥ 6 years	44 (44)	85 (32.3)	1.6 (1.02—2.6) $p = 0.039$
Occupational exposure to dusts, smokes, gases or chemicals	77 (77)	154 (58.6)	2.4 (1.4—4.0) $p = 0.001$
Former cigarette smoker	58 (58)	88 (33.5)	2.7 (1.7—4.4) $p < 0.0001$

[a] Data correspond to *n*(%).

Table 2 Family history of pulmonary fibrosis and comorbidities of cases and controls.

Characteristic	IPF cases[a] ($n = 100$)	Control subjects[a] ($n = 263$)	OR (CI95%)
Familial IPF (parent and/or sibling)	20 (20.0)	7 (2.7)	9.1(3.7—22.4) $p < 0.0001$
Past gastroesophageal reflux	23 (23.0)	23 (8.7)	3.1 (1.7—5.9) $p < 0.0001$
Past gastritis	40 (40.0)	66 (25.1)	1.9 (1.2—3.2) $p = 0.006$
Type 2 diabetes mellitus	30 (30.0)	50 (19.0)	1.8 (1.1—3.1) $p = 0.02$
Past or current cardiac disease	13 (13.0)	17 (6.5)	2.2 (1—4.6) $p = 0.05$

[a] Data correspond to *n* (%).

associated with the disease [OR = 6.1 (95% CI, 2.3—15.9) $p < 0.0001$] (Table 3). Being a former cigarette smoker, having past or current occupational exposure to dusts, smokes, gases or chemicals, and past gastroesophageal reflux were also associated with increased risk of IPF. By contrast, in this multivariate analysis, DM2, showed a tendency but it was not an independent predictor of IPF.

Discussion

Idiopathic pulmonary fibrosis is a progressive, life-threatening, lung disorder that likely arises from the interplay between genetic and environmental factors. In this context, individualization of host and environmental factors responsible for IPF predisposition and onset could play an important role for disease prevention and for devising novel therapies.

Regarding exposures, cigarette smoking has formerly been associated with sporadic IPF.[2] Furthermore, in a family-based case—control study of familial interstitial pneumonia, Steele et al[3] evaluated 111 families, with 309 affected and 360 unaffected individuals. After adjusting for age and sex, smoking was strongly related with pulmonary fibrosis. The results of the present study corroborate this association since 58% of the IPF patients were former smokers. Taken together, the evidence increasingly indicates that cigarette smoking, which among other effects generates a cumulative oxidative stress, may contribute to the pathogenesis of IPF. Interestingly, it has been shown that tobacco smoking enhances telomere shortening,[19,20] a process recently reported in most sporadic IPF patients and in a few families.[21,22] Telomeres are DNA-protein structures that protect chromosome ends from erosion and end-to-end fusion and that shorten successively with each cell division.[23] Importantly, a link between telomere length and aging-associated diseases and mortality has been suggested.[24,25] In addition, numerous associations between chronic degenerative diseases and telomere length have been reported.

Intriguingly, a putative relationship between telomere length shortening and type 2 diabetes mellitus has been recently reported.[26] Using a case—control study from a community-based population sample the association of leukocyte telomere repeat mean copy number to single gene copy number (TSR) and DM2 was examined. In a multivariable logistic regression analysis, it was found that decreased TSR [log(e)-transformed] was significantly associated with the disease. Shortened telomeres have been associated with DM2 in previous but generally small studies. DM2 has been associated with IPF in several studies involving different ethnic populations.[6—8] In this study, a tendency was also noted. However, given the high prevalence of DM2 in our adult population, a much larger study population would be necessary to provide definitive results.

As previously described, several exposures (dusts, smokes, gases or chemicals) were also associated with IPF supporting that the disease is more frequent in individuals exposed to dusty environments.[2,4,5,27] Recently, the accumulation of inorganic dusts in lung tissues of patients with IPF, chronic hypersensitivity pneumonitis, and collagen vascular diseases was analyzed by polarizing light microscopy, scanning electron microscopy and energy dispersive X-ray spectroscopy.[28] IPF lung tissues showed greater numbers of birefringent particles, even in patients without occupational exposure. The silicon/sulfur ratio and aluminium/sulfur ratio were increased in IPF independent of occupational exposure. A point elemental analysis showed that the major compound of the particles was aluminium-silicate. How tissue exposure to environmental toxicants predisposes or participates in the pathogenesis of IPF is largely unknown. However, chronic damage to alveolar/bronchiolar epithelial cells may play a role in genetically susceptible individuals.

The multivariate analysis also confirmed that gastroesophageal reflux is associated with a risk for IPF.

Table 3 Crude and adjusted odds ratios for IPF.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
Parent or sibling with IPF	9.1 (3.7—22.4) $p < 0.0001$	6.1 (2.3—15.9) $p < 0.0001$
Former smoker	2.7 (1.7—4.4) $p < 0.0001$	2.5 (1.4—4.6) $p = 0.003$
Past or current occupational exposure to dusts, smokes, gases or chemicals	2.4 (1.4—4.0) $p = 0.001$	2.8 (1.5—5.5) $p = 0.002$
Past or current gastroesophageal reflux	3.1 (1.7—5.9) $p < 0.0001$	2.9 (1.3—6.6) $p = 0.007$
Type 2 diabetes	1.8 (1.1—3.1) $p = 0.02$	1.6 (0.9—3.0) $p = 0.1$

Gastroesophageal reflux and silent microaspiration have been related with several lung diseases and is common among those who have had lung transplantation.[29] Also, a higher incidence of gastroesophageal reflux has been reported in patients with IPF compared with normal individuals suggesting that microaspiration may be a factor for IPF.[7–10] Interestingly, it has been suggested that acute exacerbation of IPF, a devastating diffuse alveolar damage manifested by some patients may be also related to microaspiration.[30]

The most remarkable finding in our study was the high prevalence of close relatives of our patients affected by pulmonary fibrosis. Thus, 20 percent of the patients had a parent and/or a sibling previously diagnosed with pulmonary fibrosis. In eight of these cases we were able to confirm the presence of pulmonary fibrosis in the family. Previous studies had estimated a significantly lower frequency of positive family history, e.g., between 0.5 and 3.7%.[11,12] However, this percentage may represent an underestimation, as evidenced by a 13 year retrospective review of the Vanderbilt Lung Transplant Program, in which 9 of 47 patients (19%) transplanted for IPF had a family history significant for interstitial lung disease.[13] Likewise, around 10% of familial IPF were recently identified within a single-center cohort of 229 patients with idiopathic interstitial pneumonias indicating that the percent of familial disease is higher than we formerly believed.[14] The majority of pedigrees indicate an autosomal dominant vertical transmission pattern of inheritance with reduced penetrance.[31] In the largest collection of familial interstitial pneumonias, 20 multigenerational pedigrees were consistent with autosomal dominant inheritance.[3]

Clinical features of familial IPF are indistinguishable from those of the sporadic form, except for an earlier age of onset.[11,12,14] This observation was confirmed in our study, with the cases with familial history presenting on average 7 years earlier than sporadic patients. Nevertheless, a potential lead time bias (in which subjects with a parent or sibling with IPF are more prone to be submitted to earlier screening and hence to have an earlier diagnosis of IPF than subjects without IPF in the family) can not be ruled-out.

Certainly, an important limitation of this study was the fact that familial history of pulmonary fibrosis was self-reported. We were able to confirm the diagnosis of IPF/IIP in only 8 of 20 patient's relatives, because the remaining parents and siblings had died when we contacted the families. However, we have no reason to suspect that the accuracy of self report of disease would be different for the other 12 patients. Also, the magnitude of the odds ratio when compared to healthy controls may be subject to some bias through over-reporting among the cases and under-reporting among controls.

In summary, we found that the presence of a familial history of pulmonary fibrosis showed the strongest association with IPF. This finding supports the notion that it is crucial to carefully evaluate and if possible corroborate the presence of family history in these patients. Exposure to tobacco smoke and other environmental smokes and dusts as well as the presence of gastroesophageal reflux also were risks to develop IPF. Although the environmental associations are not a proof of causation, our findings provide evidence that gene-environment associations are likely playing a role to trigger IPF.

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Conflict of interest

None.

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