OCCUPATIONAL AND ENVIRONMENTAL RISK FACTORS OF IDIOPATHIC PULMONARY FIBROSIS IN EGYPT

By

Awadalla NJ *, Hegazy A**, Elmetwally RA ***, Wahby I ****

*Department of Public Health and Preventive Medicine, Faculty of Medicine, Mansoura University, Egypt.

** Department of Community and Occupational Medicine, Faculty of Medicine, king Abdulaziz University, Jeddah, Saudi Arabia and Al-Azhar Univerisity, Egypt.

*** Department of Thoracic Medicine, Faculty of Medicine, Mansoura University, Egypt.

**** Department of Community and Occupational Medicine, Faculty of Medicine, Alazhar University, Egypt.

Abstract:

Background: Despite the advances in medical therapy and technology, the prognosis of idiopathic pulmonary fibrosis (IPF) remains poor and the need for disease prevention based on identifying the risk factors becomes mandatory. Occupational and environmental exposures were studied in several countries and found to play an important role in the disease development. However, in Egypt, little attention has been paid to study the effect of these factors in the disease development.

Objective: to identify the occupational and environmental risk factors associated with the development of IPF in Egypt.

Methods: A multicenter hospital- based case-control study was carried out in chest hospitals in three Egyptian Cities: Cairo, Tanta and Mansoura. Study subjects were 201 IPF confirmed cases and 205 age, sex and residence matched controls. Data on occupational and environmental factors were obtained from a questionnaire. Multiple logistic regression analysis was used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of IPF in both sexes for single factors with adjustment for age, residence and smoking status.

Results: compared with controls, the risk of IPF in male workers was observed to increase significantly in chemical and petrochemical industries and in carpentry and wood working (OR=2.56, 95%CI: 1.02-7.01) and with occupational exposures to wood dust and wood preservatives. Among female workers, a significant increase was observed in farming (OR=3.34, 95%CI: 1.17-10.12), raising birds and occupational exposures to animal feeds, products and dusts and to pesticides. Risk of IPF decreased significantly in male workers and insignificantly among female workers in sales and clerical related activities. The environmental exposures to birds and cats were significantly associated with elevated risk of IPF development in both sexes.

Conclusion: Results confirm previous studies showing positive association of IPF development and occupational and environmental dust exposures. In Egypt, farming, raising birds and wood working are important risk factors in IPF development.

Key words: case-control study, Egypt, environment, IPF, occupations.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibroproliferative disorder, which consists of the progressive fibrosis of the interstitial tissues of the lung with subsequent loss of the normal parenchymal architecture that leads to respiratory failure and death (Tsoutsou et al., 2006). In various populations, the prevalence estimates for IPF have ranged from 6 per 100,000 to as high as 32 per 100,000 (Taskar and Coultas, 2006), although this is based on case series and reports. However, more recent research has provided estimates of 20 per 100,000 adult males and 13 per 100,000 adult females and incidence figures based on these data were 10.7 and 7.4 per 100,000 per year for males and females, respectively (Baumgartner et al., 2000) .

IPF is characterized clinically by persistent dyspnea, reduced lung volumes, impaired gas exchange, and a histological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy (American Thoracic Society,2000 and American Thoracic Society/European Respiratory Society, 2002).

The etiology of IPF is still unknown as it considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, up to now supposed genes and environmental factors that consistently increases the risk of IPF have not been identified (Figueroa et al., 2010). Some studies reported potential etiologic factors of IPF including chronic exposure to domestic wood burning (Ramage et al.,1988) , atopy (Marsh et al., 1994) , Epstein-Barr virus (Vergnon et al., 1984 and Egan et al., 1995), hepatitis C virus (Ueda et al., 1992 and Irving et al., 1993) , adenovirus (Kuwano et al., 1997), and genetic factors (Bitterman et al., 1986) . Some case-control studies have focused on potential risk factors including cigarette smoking (Scott et al., 1990; Iwai et al.,1994; Hubbard et al., 1996 and Baumgartner et al., 1997), atopy (Scott et al., 1990 and Hubbard et al., 1996), and occupational and environmental exposures related to activities associated with a high probability of dust or vapor inhalation including wood dusts, metal dusts and dusts related to farming activities and raising birds (Scott et al., 1990; Iwai et al.,1994 and Hubbard et al., 1996).

Because epidemiologic information about the risk factors associated with the development of IPF in Egypt is limited, the objective of the present study is to identify occupational and environmental risk factors associated with the development of IPF, based on a multicenter hospital-based case-control study.

Subjects and methods :

Study design and location:

A multicenter hospital-based case-control study was carried out in chest hospitals and departments in three Egyptian Cities: Cairo, Tanta and Mansoura, during the period from January 2010, to January 2011.

Study population:

Cases:

All IPF confirmed cases admitted to the collaborating hospitals located in the previously mentioned cities during the study period and who agreed to participate were included in the study. The diagnosis of IPF by the respiratory disease specialists in the collaborating hospitals was based on diagnostic criteria of the American Thoracic Society and the European Respiratory Society (American Thoracic Society/European Respiratory Society, 2002) through clinical history, clinical examination, high-resolution computerized tomography (HRCT) of the chest and pulmonary function testing (PFT). None of the cases accepted to have their diagnosis confirmed through neither thoracoscopic lung biopsy nor transbronchial lung biopsy. The presence of typical clinical and HRCT features of IPF, when identified by expert clinicians and radiologists, is sufficiently characteristic to allow a confident diagnosis and eliminate the need for surgical lung biopsy (American Thoracic Society/European Respiratory Society, 2002). All cases had basal fine crackles by auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis on HRCT. Abnormal pulmonary function revealed evidence of restriction (reduced VC with an increased FEV1/FVC ratio).There was no evidence of either coexisting collagen-vascular disease or history of known occupational exposure to agents that might produce a clinical picture similar to that of IPF in any of the cases. The physicians in charge asked eligible patients to participate in this study, and 201 patients were cooperative in answering the questionnaires while 19 patients refused.

Controls:

One control subject was selected to match each case in age (±3years), sex, residence and smoking habits from patients admitted to the same wards, during the same period and treated from respiratory diseases other than interstitial pulmonary fibrosis. Out of the 220 controls, only 205 subjects accepted to participate in the study.

The study was approved by the Research Ethics Committee of Mansoura Faculty of Medicine. Written informed consent was taken from each subject included in the study.

Data collection:

All data were collected by interview through two questionnaires. One of the questionnaires collected information from both cases and controls about personal history as age, sex, marital status, residence, educational level, smoking habits, type of job and exposure to 11 specific occupational agents and environmental exposures as moulds in the house and indoor domestic pets. Occupational data focused on type of job held for the longest period of time during the subject's work life and years of exposure. Occupational agents were defined as present if the subject reported >10 h of exposure per week. The other questionnaire was used to collect the clinical criteria of IPF patients, results of chest radiography (plain and HR CT), pulmonary function testing, bronhoalveolar lavage and biopsy whenever done and investigations done to exclude collagen diseases.

Statistical analysis:

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 11 (SPSS Inc., Chicago, IL, USA). Both study groups were compared using the chi-square test for qualitative variables and student's t-test for quantitative variables. Multiple logistic regression analysis was used to estimate the adjusted ORs and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, residence and smoking for both males and females.

The reference category for job title, occupational and environmental factors was based on the comparison of those exposed to a single agent with all those unexposed, including potential subjects who were exposed to other etiologic factors.

Results

Table 1 summarizes the demographic data of the studied groups. Both groups were matched in sociodemographic characteristics. In the IPF patients, the age ranged from 22 to 78 years (mean: 51.04±10.45), most of patients (51.70%) belonged to the 45-to 59 year age group. The patient group contained more females (52.70%), residents of rural areas (41.30%), never smokers (70.10%) and patients with low educational level (50.70%)

Clinical and laboratory characteristics of IPF patients were presented in table 2. The mean disease duration was 30.49 ± 26.28 month. At the time of admission in the chest department, most of them were in grade IV dyspnea (53.20%), grade I clubbing (69.2%) and all of them had central cyanosis and bibasilar dry crackles. Ground glass appearance on chest CT scan was observed also, in all cases. Reduction in the FVC percentage of predicted was detected in all patients with mean of (62.44±13.01%) also normal or high FEV1/ FVC ratio % was observed in all patients with mean of (102.72±11.16). Additionally, the average PaO2 and O2 sat were found reduced (72.83±10.47 and 85.17±13.35, respectively).

Table 3 presents the adjusted ORs and 95% CIs for IPF in relation to occupational groups after controlling for age, residence and smoking. Among male workers, the risk of IPF was observed to increase significantly in chemical and petrochemical industries (OR=6.47, 95% CI: 1.66-25.12) as well as carpentry and wood working (OR=2.56, 95%CI: 1.02-7.01) and to decrease significantly in activities related to sales (OR=0.11, 95%CI: 0.02-0.54) and clerical works (OR=0.21, 95%CI: 0.02-0.52). Among female workers, the risk was observed to increase significantly in farming (OR=3.34, 95%CI: 1.17-10.12) as well as raising birds (OR=1.82, 95%CI: 1.03-3.85).

The occupational exposures associated with the development of IPF after controlling of age, residence and smoking were demonstrated in table 4. For male workers, occupational exposures to wood dust and wood preservatives were observed to significantly increase the risk of IPF development (OR=2.71, CI: 1.01-7.37).

In female workers, on the other hand, the risk of IPF development was significantly increased with occupational exposures to animal feeds, products and dust (OR= 1.78, CI:1.01-3.13) as well as pesticides (OR= 8.68, CI:1.04-72.17).

Lastly, as shown in table 5, the environmental exposures to birds and cats were significantly associated with elevated risk of IPF development in both males (OR=3.49, CI:1.49-8.19 and OR= 6.38, CI:1.59-25.56 respectively) and females (OR=3.86, CI:1.95-7.62 and OR=8.24, CI:1.80-37.70) after controlling age, residence and smoking. On the other hand the presence of moulds at home was not significantly associated with IPF development.

Table 1. Sociodemographic criteria of studied groups

	Cases (n=201)	Controls (n=205)	Test of significance	P- value
Age mean ± SD	51.04 ±10.45	50.26±10.41		
<30	7(3.5%)	6(2.9%)	t = 0.75	0.45
30-44	54(26.9%)	62(30.2%)		
45-59	104(51.7%)	105(51.2%)	χ^2 = 0.82	0.84
≥ 60	36(17.9%)	32(15.6%)		
sex :				
Male	95(47.30%)	114(55.60%)	χ^2 = 2.83	0.11
Female	106(52.70%)	91(44.40%)		
Marital status:				
Married	186(92.50%)	178(86.80%)	χ^2 = 3.56	0.07
Single	15(7.50%)	27(13.20%)		
Residence:				
Urban	77(38.30%)	64(31.20%)		
Suburban	41(20.40%)	49(23.90%)		
Rural	83(41.30%)	92(44.90%)	χ^2 = 2.33	0.31
Smoking:				
Smoker	52(25.90%)	64(31.20%)		
Ex-smoker	8(4.00%)	3(1.50%)		
Non- smoker	141(70.10%)	138(67.30%)	χ^2 = 3.50	0.17
Types of smoking:				
Cigarette	52(89.70%)	51(76.10%)	χ^2 = 3.92	0.06
Goza/shesha	6(10.30%)	16(23.90%)		
Packs/year mean ± SD	380.06±186.98	331.65±195.48	Z=1.3	0.19
Duration (years)	23.27±9.41	23.95±9.64	t=0.39	0.69
Educational level:				
Low	50.70%))102	98(47.80%)		
Moderate	36.30%))73	90(43.90%)		
High	12.90%))26	17(8.30%)	χ^2 = 3.69	0.15

Table 2. Clinical and laboratory characteristics of IPF patients

	Cases (n=201)
Duration in month (mean ±SD)	30.49 ± 26.28
Dyspnea	
Grade I	3(1.49%)
Grade II	45(22.38%)
Grade III	46(22.88%)
Grade IV	107(53.23%)
Clubbing	
Grade I	127(63.18%)
Grade II	62(30.85%)
Grade III	12(5.97%)
Central Cyanosis	201(100%)
Bibasilar dry crackles	201 (100%)
Ground glass appearance on chest radiograph	201(100%)
[a]PFTs, % of predicted	
FVC	62.44±13.01
FEV_1	66.23±14.03
FEV_1/ FVC	102.72±11.16
Arterial blood gases	
pH	7.35±0.05
$PaCO_2$	40.71±12.14
HCO_3	24.13±9.00
PaO_2	72.83±10.47
O_2sat	85.17±13.35

aPFTs= Pulmonary Function Tests

Table 3. Associations of occupational groups ¥ with IPF development in male and female populations.

Occupational groups	Male				Female			
	Control (n=114)	Cases (n=95)	OR‡ (95%CI)	p-value	Control (n=91)	Cases (n=106)	OR (95%CI)	p-value
Clerical	11(9.60)	3(3.20)	0.21 (0.02-0.52)	0.02*	9(9.90)	0(0.00)	-	0.65
Sales	17(14.90)	2(2.10)	0.11 (0.02-0.54)	0.005*	7(7.70)	3(2.80)	0.35 (0.07-2.78)	0.27
Farming	28(24.60)	20(21.10)	1.00 (0.44-2.28)	0.98	7(7.70)	22(20.80)	3.34 (1.17-10.12)	0.02*
Fishing	4(3.50)	3(3.20)	1.11 (0.22-5.60)	0.89	5(5.50)	3(2.80)	0.52 (0.11-2.33)	0.39
Hairdressing	1(0.90)	2(2.10)	1.89 (0.15-22.87)	0.61	10(11.00)	11(10.40)	1.01 (0.37-2.70)	0.97
Construction and Building demolition	14(12.30)	11(11.60)	0.96 (0.39-2.37)	0.93	-	-	-	-
Mechanics	12(10.50)	10(10.50)	0.96 (0.37-2.47)	0.94	-	-	-	-
Carpentry or woodworking	7(6.10)	14(14.70)	2.56 (1.02-7.01)	0.05*	2(2.20)	8(7.50)	3.48 (0.67-18.16)	0.13
Chemical/ petrochemical	3(2.60)	12(12.60)	6.47 (1.66-25.12)	0.007*	1(1.10)	2(1.90)	2.06 (0.17-23.89)	0.65
Painting	12(10.50)	6(6.30)	0.57 (0.20-1.62)	0.29	-	-	-	-
Raising birds	1(0.90)	3(3.20)	3.37 (0.31-36.16)	0.31	18(19.80)	35(33.00)	1.82 (1.03-3.85)	0.05*
Textile making	2(1.80)	5(5.30)	2.76 (0.45-15.57)	0.25	7(7.70)	4(3.80)	0.63 (0.17-2.35)	0.49
Housewife	-	-	-	-	23(25.30)	28(29.4)	0.77 (0.38-1.57)	0.48
Others	2(1.80)	6(6.40)	2.39 (0.40-14.30)	0.33	4(4.40)	3(2.70)	0.23 (0.02-2.13)	0.19

¥ Adjusted for age, residence and smoking (ever/ never)

‡OR=odds ratio, CI= Confidence interval.

*Statistically significant (P≤0.05)

** Highly statistically significant (P≤0.001)

Table 4. Associations of occupational exposures ¥ with IPF development in male and female populations.

Occupational exposures	Male				Female			
	Control (n=114)	Cases (n=95)	OR‡ (95%CI)	p-value	Control (n=91)	Cases (n=106)	OR (95%CI)	p-value
Animal feeds, products and dust	27(23.7)	16(16.8)	0.65 (0.32-1.30)	0.23	42(46.2)	64(60.37)	1.78 (1.01-3.13)	0.04*
Foods (vegetables, fruits, meat, fishes, seafood, ,..)	4(3.5)	2(2.1)	.48 (0.08-2.82)	0.41	2(2.2)	1(0.9)	1.01 (0.06-16.96)	099
Wood dust , wood preservatives	7(6.1)	15(15.8)	2.71 (1.01-7.37)	0.04*	2(2.2)	8(7.5)	4.32 (0.84-22.12)	0.08
Insecticides/pesticide	6(5.3)	8(8.4)	2.24 (0.72-7.28)	0.17	1(1.1)	9(8.5)	8.68 (1.04-72.17)	0.04*
Stone, clay, glass, concrete…	14(12.3)	12(12.6)	1.11 (0.45-2.72)	0.87	0(0.00)	2(1.9)	-	0.79
Metal dust/welding fumes	15(13.2)	17(17.9)	1.58 (0.69-3.61)	0.27	-	-	-	-
Solvents	12(10.5)	12(12.6)	1.06 (0.44-2.59)	0.88	0.00))0	1(0.9)	-	0.84
Hair dyes	1(0.9)	2(2.1)	1.89 (0.15-22.87)	0.61	11(12.1)	11(10.4)	0.89 (0.34-2.31)	0.81
textile dust	2(1.8)	6(6.3)	3.25 (0.60-17.56)	0.16	10(11.0)	4(3.8)	0.40 (0.11-1.38)	0.14
others	2(1.8)	6(6.3)	3.15 (0.56-17.61)	0.19	3(3.3)	2(1.9)	0.64 (0.10-4.06)	0.64

¥ Adjusted for age, residence and smoking (ever/ never)
‡OR=odds ratio, CI= Confidence interval.
*Statistically significant (P≤0.05)
** Highly statistically significant (P≤0.001)

Table 5. Associations of environmental exposures ¥ with IPF development in male and female populations.

Environmental Exposures	Male				Female			
	Control (n=114)	`Cases (n=95)	OR‡ (95%CI)	p-value	Control (n=91)	Cases (n=106)	OR (95%CI)	p-value
Birds	12 (10.5)	22 (23.2)	3.49 (1.49-8.19)	0.004*	25 (27.5)	59 (55.7)	3.86 (1.95-7.62)	0.000**
Cats	3 (2.6)	10 (10.5)	6.38 (1.59-25.56)	0.009*	2 (2.2)	15 (14.2)	8.24 (1.80-37.70)	0.007*
Dogs	6 (5.3)	8 (8.4)	1.94 (0.61-6.12)	0.25	2 (2.2)	8 (7.5)	3.63 (0.75-17.56)	0.11
Moulds[a]	19 (16.6)	15 (15.7)	0.68 (0.30-1.45)	0.26	23 (25.2)	25 (23.6)	1.37 (0.71-2.36)	0.34

¥ Adjusted for age, residence and smoking (ever/ never)

‡ OR=odds ratio, CI= Confidence interval.

*Statistically significant (P≤0.05)

** Highly statistically significant (P≤0.001)

a any home place moulds

Discussion

The present case-control study demonstrated the associations of some occupational and environmental factors in the development of IPF in the Egyptian population. The risk of IPF was found to be increased among male workers in carpentry or woodworking and chemical and petrochemical industry. Chemical fumes and dusts were accused by several studies in the development of IPF (Scott et al., 1990; Mons et al., 1991; Iwai et al., 1994; Hubbard et al., 1996 and Baumgartner et al., 1997). Although the mechanism is not well understood, it may be through their fibrogenic activity related to activation of oxygen species (Lison et al., 1996). Also genetic susceptibility (Nemery et al., 2001and Wahidi et al., 2004) and overwhelming of lung clearance mechanisms (Churg et al., 1996) are important contributing factors. Wood dust, as well as chemicals for wood protection, wood adhesives, and moulds present in wood, may contribute to an increase in fibrosis or extrinsic allergic alveolitis (Scott et al., 1990; Hubbard et al., 1996; Baumgartner et al., 1997; Mullen et al., 1998; Miyake et al., 2005 and Gustafsson et al., 2007).

In the present study farming and raising birds with the potential exposures to dusts of animal feeds, products and waste as well as pesticides were significant risk factors of IPF development among female workers. Also, the environmental exposure to domestic birds and cats was positively associated with IPF development in both genders. These findings were in accordance with Baumgartner et al., 1997; Iwai et al., 1994 and Gustafsson et al., 2007 .

Agricultural workers are exposed to very high levels of dust and aerosolized particulates from a variety of sources, including feed grains, bedding, and livestock fecal material (Craighead et al., 1995), and tend to have an increase in the prevalence of lung fibrosis (Liebertrau G,1990) .

In Egypt, the poultry industry has expanded rapidly over the past 25 years to provide approximately 55% of the per capita animal protein consumption. Problems with raising birds in Egypt include; widespread roof-top and back-yard raising bird, unhygienic local marketing and home slaughtering as well as the presence of approximately 40,000 poultry farms lacking biosecure and hygienic production systems and unprotected exposure to birds (Kaoud HA, 2008 and

WHO, 2010). These widespread unplanned and unprotected activities in raising birds and their environmental impacts help in magnifying the role of raising birds in IPF development. In Egypt, women were found to be more involved in raising birds than male and this may explain the elevated risk of IPF in females (Nanees and Hanaa, 2010).

The risk of IPF development was significantly low in males and insignificantly among females working as sellers and clericals. These findings were in agreement with Miyake and Colleagues (2005) and may support the hypothesis of positive associations of IPF with dust-exposed occupations (Coultas et al., 1994).

Study limitations

There are several limitations to our study. First, the case-control study design. Second, the study was conducted in three Egyptian cities only. Third, the patients were not confirmed by lung tissue biopsy. In addition, the study did not provide the investigations regarding biological mechanisms of IPF development

Despite these limitations, the consistency of the observed positive associations of IPF development and working in occupations with dust exposure as wood working, chemical industries, farming and raising birds and the potential occupational exposure to dusts of wood, pesticides and animals and the environmental exposures to dusts of birds and cats, may strengthen these associations and minimize the possibility of bias related to case control study. Furthermore, the study was multicenter carried out in three Egyptian Cities of different population's demographic, occupational and environmental charcterstics, therefore it may be considered as a valid approach for studying occupational and environmental risk factors in Egypt.

Conclusion

The present study confirms the results from previous epidemiologic studies about the positive association of IPF development and occupational and environmental dust exposures. In Egypt, farming, raising birds and wood working are important risk factors in IPF development after adjustment of age, smoking and residence.

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