Scope on idiopathic pulmonary fibrosis in Upper Egypt

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Background Clinical features of idiopathic pulmonary fibrosis (IPF) are not the same in all patients and are characterized by being nonspecific. Symptoms range from nothing at all to severe disabling dyspnea.

Aim To explore the demographic, clinical and physiological characteristics of IPF patients attending the outpatient clinic at El-Minia and Assiut University Hospitals to see whether they match with or differ from the common features of the disease known worldwide.

Patients and methods One hundred-twenty six patients diagnosed as IPF underwent detailed history taking, clinical examination, spirometery, oxygen saturation and trans-thoracic echocardiography.

Results About 43% of patients developed IPF before age of 50 and the mean age at time of diagnosis was 48.6 ± 12.9 years. Eighty four (66.7%) patients were males. Ninety (71.4%) patients had significant tobacco smoke exposure. Dyspnea was present in 120 (95.2%) patients and the majority had grade 3 and 4 dyspnea. Ninety-five percentage of patients had cough. Clubbing of fingers was present in 72 (57.1%). All patients had bilateral basal crepitation. The mean of FVC was 52.5 ± 15.2% while the mean O_2 saturation was 91.9 ± 4.8%. One third of patients (33.3%) had corpulmonal and those have significantly longer duration of illness and significantly lower FVC and O_2 saturation ($P < 0.001$ for each).

Conclusion In our locality IPF patients had younger age of presentation while other demographic, clinical and physiological features were more or less similar to those recorded worldwide.

Egypt J Broncho 2015 9:154–159

Egyptian Journal of Bronchology 2015 9:154–159

Keywords: clubbing, cor pulmonale, dyspnea, idiopathic pulmonary fibrosis

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Received 8 November 2014 **Accepted** 5 December 2014

Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) [1–3]. There is some general consensus worldwide about its clinical presentation and demographic features. Most published data indicate that IPF primarily occurs after the age of 50 and that it is more common in men than in women [4,5]. Even after encountering a typical UIP pattern in patients less than 50 years and even if lacking any clinical feature of connective tissue disease, many authors still deny the diagnosis of IPF in this age group and suggest connective tissue disease that is subclinical as the cause of UIP [6,7]. The clinical symptoms of IPF are nonspecific. Exertional dyspnea and nonproductive cough are the most common symptoms of IPF. Unfortunately they can be shared by a myriad of diagnoses — for example, cardiac diseases, chronic obstructive pulmonary disease, and many others. Systemic symptoms like weight loss, low-grade fever, fatigue, arthralgia, or myalgia can occur but are uncommon. About 5% of IPF patients are asymptomatic at the time of diagnosis and are discovered incidentally [8]. Digital clubbing is seen in 25–50% of patients with IPF. Bibasilar fine inspiratory crackles (Velcro crackles) are encountered in most IPF patients [4]. Pulmonary hypertension is encountered in 20–40% of patients with IPF who are evaluated or listed for lung transplantation [9].

Patients and methods

Study participants

The study targeted any IPF patient attending the outpatient clinic of Chest Departments at El-Minia and Assiut University Hospitals during the period from May 2013 to June 2014. A total of 126 IPF patients were randomly recruited. The diagnosis of IPF was made according to the ATS/ERS/JRS/ALAT statement (2011) [10]. The study was approved by the Regional Ethical Committees of El-Minia and Assiut Universities and informed consent was obtained from all patients before enrollment.

Patient selection

Inclusion criteria

The study enrolled patients who had a confirmed diagnosis of IPF according to the ATS/ERS/JRS/ALAT statement (2011) [10]. The diagnosis of IPF required the following:

(a) Exclusion of other known causes of interstitial lung disease (ILD) (e.g. domestic and occupational

environmental exposures, connective tissue disease, and drug toxicity);
(b) Presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy; and
(c) Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

Exclusion criteria

(1) ILD other than IPF, such as:
   (a) When there is clinical and/or laboratory evidence of connective tissue disorder.
   (b) When the disease is caused by occupational or environmental exposure.
   (c) When the patient is receiving drugs that may cause ILD.
(2) Evidence of mixed pulmonary dysfunction on spirometry.

All patients were subjected to detailed history taking, full clinical examination, pulse oximetry, and basic pulmonary function test using portable spirometry and echocardiography. Dyspnea was graded from 0 to 4 according to the modified medical research council dyspnea scale (mMRC scale) [11]. Clubbing was graded up to 4° [12]. Pulmonary hypertension was confirmed when transthoracic pulmonary artery systolic pressure was more than 40 mmHg [13].

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 17 (SPSS Inc., Chicago, Illinois, USA). Continuous data were expressed as mean ± SD and compared using Student's *t*-test and analysis of variance test. Categorical variables were expressed as percentage and compared using the χ^2-test. Spearman's correlation coefficient was calculated to quantify the correlation between variables. *P*-value less than 0.05 was considered statistically significant.

Results

A total of 126 patients fulfilled the criteria for IPF and were enrolled in the study. Table 1 shows the characteristics of the studied patients. About two-third were male and more than 70% of patients were smokers. Forty-three IPF patients were less than 50 years old and the age at the time of diagnosis was 48.6 ± 12.9 years (Table 1). The frequency of IPF was most common in patients above 60 years (Table 2). Most patients had cough and dyspnea and the majority had grade 3 or 4 dyspnea. There was significant positive correlation between dyspnea grade and the duration of illness and a significant negative correlation between dyspnea grade and forced vital capacity (FVC) and O_2 saturation (Table 3). Clubbing of fingers was present

Table 1 Demographic, clinical, and physiological data of the studied patients (*n* = 126)

Variables	Mean ± SD or *n* (%)
Age (years) at time of the study	53.4 ± 11.8
<50	54 (42.9)
≥50	72 (57.1)
Age at time of diagnosis (years)	48.6 ± 12.9
Sex	
Male	84 (66.7)
Female	42 (33.3)
Smoking status	
Current smoker	6 (4.8)
Nonsmoker	36 (28.6)
Ex-smoker	60 (47.6)
Passive smoker	24 (19)
Biomass fuel	12 (9.5)
Duration of illness (years)	4.1 ± 2.5
Clubbing	
Present	72 (57.1)
Absent	54 (42.9)
Dyspnea grades	
G0	6 (4.8)
G1	12 (9.5)
G2	24 (19)
G3	30 (23.8)
G4	54 (42.9)
Cough	
No	6 (4.8)
Dry	24 (19)
Productive	96 (76.2)
Wheeze	48 (38.1)
Crepitation	126 (100)
Rhonchi	36 (28.6)
Lower limb edema	24 (19)
O_2 saturation	91.9 ± 4.8
FVC (l/m)	52.5 ± 15.2
GERD	60 (47.6)
Cor pulmonale	42 (33.3)

FVC, forced vital capacity; GERD, gastroesophageal reflux disease.

Table 2 Frequency of idiopathic pulmonary fibrosis on the basis of age

Age group (years)	Frequency (%)
20–30	6 (4.8)
30–40	12 (9.5)
40–50	30 (23.8)
50–60	36 (28.6)
>60	42 (33.3)
Total	126 (100)

Table 3 Correlation of duration of illness, O_2 saturation, and forced vital capacity with dyspnea grades

	Dyspnea grades	
	r	*P*-value
Duration of illness (years)	0.462	<0.001
O_2 saturation (%)	−0.648	<0.001
FVC (l/m)	−0.566	<0.001

FVC, forced vital capacity.

in 57% of patients and there was a positive correlation between the degree of clubbing and duration of illness and negative correlation with FVC and O_2 saturation (Table 4). All patients had crepitations heard at lung bases, whereas rhonchi were present only in 28% of patients (Table 1). All patients had restrictive pulmonary dysfunction and the mean FVC was 52.5 ± 15.2 l/m, whereas the mean O_2 saturation was 91.9 ± 4.8%. One-third of patients had cor pulmonale (Table 1) and these patients had significantly longer duration of illness and significantly lower FVC and O_2 saturation (Tables 5 and 6).

Discussion

IPF is a progressive and severely debilitating lung disease associated with high mortality. IPF is characterized by inflammation and scarring of lung tissue and loss of lung function over years [10].

In the present study IPF was seen to occur in both sexes but was more common among men than among women (66.7 vs. 33.3%). This is in agreement with many studies that tackled the sex incidence of IPF [1,4,5,14] and found that, although IPF affects both sexes, it occurs more frequently in men than in women. Again in agreement with most of the epidemiologic studies on IPF performed worldwide [1,4,5,14], the majority of patients enrolled in this study were elderly (the mean age at the time of enrollment in the study was 53.4 years) and the disease was encountered more frequently above the age of 60 years (33.3%).

Table 4 Correlation of duration of illness, O_2 saturation, and forced vital capacity with clubbing

	Clubbing	
	r	*P*-value
Duration of illness (years)	0.004	0.966
O_2 saturation (%)	−0.142	0.113
FVC (l/m)	−0.156	0.08

FVC, forced vital capacity.

Table 5 Duration of illness, forced vital capacity, and O_2 saturation as regards the presence or absence of cor pulmonale

	Patients with cor pulmonale (*n* = 42)	Patients without cor pulmonale (*n* = 84)	*P*-value
Duration of illness (years)	5.9 ± 2.8	3.3 ± 1.9	<0.001
FVC (l/m)	44.7 ± 16.7	56.4 ± 12.7	<0.001
O_2 saturation (%)	88.7 ± 5.5	93.5 ± 3.3	<0.001

FVC, forced vital capacity.

Looking more carefully to the age incidence of IPF in the present work we noticed that about 43% of our patients developed IPF before age of 50 years and the average age of diagnosis was 48 years which is younger than the reported in many literatures where the average age of diagnosis was around 60-year [15,16]. Moreover, these findings do not match the statement mentioned in the ATS document (2011); patients with IPF aged less than 50 years are rare; such patients may subsequently manifest overt features of an underlying connective tissue disease that was subclinical at the time of diagnosis of IPF [10]. The relatively higher incidence of IPF in individuals younger than 50 years in our locality, compared with most other countries, necessitates more studies including a larger number of patients to prove or disprove our results. These results should also encourage more studies on the air we breathe in this area, and even nationwise.

What was interesting during the course of this study is that we encountered many young patients, especially women, diagnosed with IPF. However, by meticulous history taking and connective tissue profile analysis we found that most of these women either had significant environmental exposure or had highly positive serology for connective tissue disease. These patients were excluded from the present study and thus cannot be considered as a cause for the relatively high incidence of IPF in patients less than 50 years in this work. Generally speaking, the older age at presentation of IPF may be due to the fact that the process of pulmonary fibrosis resulting from lung injury, inflammation, and scarring takes a long time to cause significant destruction to lung tissue and loss of lung function with subsequent clinical manifestation [17]. The male predominance in the disease may be due to cigarette smoking, which may play a role in the pathogenesis of the disease, as we found that 71.4% of our patients were exposed to tobacco smoke either as current smokers, ex-smokers, or passive smokers, whereas only 28.6% were nonsmokers. Oxidant stress from smoking may damage alveolar epithelial cells and contribute to the pathogenesis of IPF. This finding was compatible with that of many authors who reported that the majority of IPF patients had a history of cigarette smoking [14,18–22]. Other authors while studying the relation between cigarette smoking and IPF reported that, although cigarette smoking plays a role in the development of pulmonary fibrosis, it has actually extended survival in some patients, compared with nonsmoking or being a former

Table 6 Relation between smoking status, forced vital capacity, and O_2 saturation

Smoking status	Nonsmoker (*n* = 36)	Ex-smoker (*n* = 60)	Passive smoker (*n* = 24)	Current smoker (*n* = 6)	*P*-value
FVC	54.3 ± 14.6	51.8 ± 13.2	47.8 ± 19.7	68 ± 13.4	0.024
O_2 saturation	92.8 ± 4.3	91.8 ± 4.9	89.8 ± 4.9	96 ± 4.6	0.012

FVC, forced vital capacity.

smoker. A likely explanation is that these patients may seek medical attention earlier for smoking-related symptoms. However, inconsistent with this result, we found that current smokers with IPF had significantly greater FVC (68 ± 13.4 vs. 54.3 ± 14.6 in nonsmoking IPF patients), more oxygen saturation (96 ± 4.6 vs. 92.8 ± 4.3%), and greater third-degree digital clubbing.

Exposure to biomass smoke was explored because in some rural areas biomass is still used for cooking and heating. Only 9.5% of our patients were exposed to biomass smoke. This comes in agreement with the results of Garcia-Sancho *et al*., who explored the link between biomass exposure and the development of IPF in a case–control study including 97 IPF Mexican patients and revealed no significant association [17]. Exposure to biomass has been related to pulmonary fibrosis in some studies and case reports. A case–control study by Scott *et al*. [19] revealed dust exposure including biomass in 27 patients out of 40 with cryptogenic fibrosing alveolites, indicating a highly significant association.

Digital clubbing was recorded in 57.1% of our patients. This is in agreement with the results of many other studies, which have reported an incidence of clubbing in 25–50% of patients with IPF [23]. Kanematsu *et al*. [24] reported clubbing in 67% of the 55 IPF patients included in their study. Moreover, several authors stated that, among different ILDs, IPF represents the most common cause of digital clubbing. IPF also represents the most common pulmonary cause of digital clubbing in developed countries [25]. In our study, digital clubbing was significantly more common in male patients and was positively correlated with the duration of illness and negatively correlated with FVC and O_2 saturation. This may support the hypoxic theory of fine bibasilar crackles (Velcro rales) being seen in all patients in the present study. The presence of these crackles is characteristic of IPF; a survey on IPF involving 149 physicians from European countries reported Velcro crackles at lung bases in almost all IPF patients [26]. Recent guidelines for diagnosis and clinical management of IPF report that fine crackles have excellent sensitivity and good specificity for the disease process of pulmonary fibrosis and thus advocate that lung auscultation is valuable in the early diagnosis of IPF. It may be attributed to the sudden opening of abnormally closed small airways and fibrotic alveoli [27].

Dyspnea is the hallmark symptom of IPF and the disease should be considered in all adult patients with unexplained chronic exertional dyspnea [4]. Dyspnea in IPF is characterized by progressive worsening over years and is associated with a poor prognosis. In this study there was a statistically significant positive correlation between MRC dyspnea scale and the duration of illness (r = 0.462 and P < 0.001) and a statistically significant negative correlation between mMRC dyspnea scale and both FVC (r = −0.566 and P < 0.001) and O_2 saturation (r = −0.648 and P < 0.001). Spyros *et al*. [28] studied the association of MRC chronic dyspnea scale scores with lung function indices in 26 IPF patients. The study estimated a statistically significant association between MRC dyspnea scores and FVC and PaO_2 and other pulmonary function indices. They reached the conclusion that the MRC dyspnea scale could offer useful information about disease severity in IPF patients.

Collard *et al*. [29] studied the 12-month changes in dyspnea score, FVC, and oxygen saturation in 51 IPF patients. The study denoted progressive worsening of dyspnea score, FVC, and O_2 saturation over time. This can indirectly support the negative correlation estimated in the present study between the duration of illness and both FVC and O_2 saturation.

Reflux may cause microaspiration of gastric contents, which is injurious to the alveolar epithelium, and this injury may cause inflammation, scarring, and fibrosis [30].

Nearly half of the patients in the present study had gastroesophageal reflux disease (GERD) depending on their symptomatology. In agreement with this, Lee *et al*. [31] encountered GERD in the patients' history in 34–45% of participating IPF patients. The same study reported survival benefit of about 3 years when giving GERD treatment. Other studies reported a higher incidence of GERD in IPF patients (about two-third), but these studies used esophageal manometry and 24-h pH monitoring to objectively diagnose GERD [32]. Spirometry revealed a restrictive pulmonary dysfunction in all patients participating in the present study, which is essential to diagnose IPF. Moreover, FVC was found to be negatively correlated with the duration of illness, dyspnea score, and pulmonary artery systolic pressure and positively correlated with O_2 saturation. Xaubet *et al*. [33] studied the correlation between disease severity as assessed by HRCT on one hand and FVC on the other in 39 IPF patients. The study estimated a significant correlation between FVC and HRCT and this refers to the value of FVC in evaluating the severity of the disease in IPF patients. A decline in FVC has consistently been used as a strong predictor of mortality, and is also frequently used as an endpoint in clinical trials. A decline in FVC of at least 10% over a 6-month period is associated with about five-fold increase in the risk of mortality [29].

In the present study oxygen saturation was negatively correlated with the duration of illness. Further, desaturation was associated with an increase in dyspnea score and a decrease in FVC. Nishiyamaa *et al.* [34] revealed a significant correlation between oxygen saturation on the one hand and both the baseline dyspnea index score and the total SGRQ score on the other, leading to the assumption that oxygen saturation might have an influence on dyspnea, which is consistent with the present study.

Pulmonary hypertension and cor pulmonale were detected in one-third of our patients. The pathobiology of PH in IPF is incompletely understood and research groups have only recently started to focus on the vascular aspects of chronic lung fibrosis. The results of recent clinical studies do not support the hypothesis that the predominant mechanisms for the development of PH in IPF are hypoxic vasoconstriction and pulmonary capillary loss after scar tissue accumulation: the presence of PH cannot be explained in all patients with IPF on the basis of hypoxemia or degree of lung function reduction [35–37].Our results coincide with several others that have found that the prevalence of PH in patients with IPF is between 32 and 85%, and PH seems to develop over time in most patients with IPF [38,39].

Acknowledgements

Conflicts of interest

None declared.

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