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Features and outcome of familial idiopathic pulmonary fibrosis

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Abstract. *Background:* Idiopathic pulmonary fibrosis (IPF) has a sporadic occurrence in most instances, but can also occasionally occur in familial form. While clinical features of sporadic IPF are well defined, clinical presentation, complications, and outcome of familial IPF are still undefined. This retrospective study was undertaken to establish clinical parameters and survival time in a consecutive series of patients with familial IPF and to establish whether the phenomenon of anticipation could be observed. *Methods:* 30 patients had received a diagnosis of familial IPF at our institution over the period from January 2005 and December 2011; in 7 of them there was a parent–child relation. Clinical features and patient outcome were analyzed and contrasted to a well characterized cohort of 127 patients with non familial IPF. *Results:* there was no significant difference in presenting symptoms and the overall outcomes were quite similar in the two groups, but the familial group was much more enriched for females and we found a statistically significant lower age at onset in the younger generations (mean age 57,8 years versus 74,2 years, p 0,001). *Conclusion:* familial IPF seems indistinguishable from sporadic IPF with respect to most clinical and physiologic findings; however the age of onset was slightly lower among the familial cases than in the sporadic cases of IPF and the phenomenon of anticipation could be observed. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 28-36)*

Key words: Familial idiopathic pulmonary fibrosis, Interstitial pneumonia, IPF, Anticipation

Introduction

Idiopathic pulmonary fibrosis (IPF) has a sporadic occurrence in most instances, but can also occasionally occur in familial form. Marshall et al estimated that familial cases account for 0,5% - 2,2% of IPF cases and reported the prevalence of familial pulmonary fibrosis as 1,34:1.000.000 population (1); more recent studies suggest that 2 – 36% of IPF is familial with up to 19% of persons with IPF reporting a family history significant for interstitial lung disease (2, 3). Familial IPF has previously been defined in the literature with various criteria including the following: patients with clinical features compatible with IPF in combination with either compatible high-resolution computed tomography (HRCT) scan findings or histological evidence of UIP (usual interstitial pneumo-

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nia) found on lung biopsy specimens in two or more family members; in an index case with at least two other affected relatives (4); or as IPF in at least two first-degree relatives (5). While clinical features of sporadic IPF are well defined (6), regarding familial IPF, the clinical presentation, complications, and outcome of patients are still undefined issues and it has yet to be proven whether familial forms of IPF have a particularly different natural history because of genetic influence or other factors. Several publications have compared familial and sporadic IPF and no distinguishing features have emerged a part from a younger age at diagnosis (1, 7-11). The phenomenon characterized by the onset of the disease at an earlier age or a greater disease severity in successive generations is known as "genetic anticipation" and it is a widely known characteristic of many diseases with genetic inheritance (12-18). Furthermore, there are no data in the current literature about the prevalence of familial IPF in Italy.

The current study was undertaken to establish clinical parameters and survival time in a consecutive series of patients with familial IPF. Herein, we report our experience with all patients with documented familial IPF (F-IPF) who were seen at the Morgagni – Pierantoni Hospital (Forlì, Italy) over a 7 year period. In particular, clinical features and patient outcome were analyzed and contrasted to a well characterized cohort of patients with non familial IPF from our institution. Finally, within the familial IPF group, we selected pairs of patients from different generations belonging to the same family and we compared the age of initial diagnosis between the members of each pair to establish if the phenomenon of anticipation could be observed.

Materials and methods

Using the Morgagni-Pierantoni Hospital database, the records of all patients who had received a diagnosis of familial IPF over the period from January 2005 to December 2011 were reviewed. Clinical features and patient outcome were analyzed and contrasted to a well characterized cohort of 127 patients with non familial IPF, who had received a diagnosis of IPF from our institution in the same period. Families in whom on patient had IPF and another member had non specific interstitial pneumonitis (NSIP) or another IIP were excluded from the study design. Diagnosis of IPF was accepted if compatible clinical features were present in combination with either HRCT scan findings in patients not subjected to surgical lung biopsy or specific combinations of HRCT and histological criteria (19, 20). Clinical criteria for a diagnosis of IPF included the presence of typical bibasilar end-inspiratory crackles, finding of a restrictive defect on pulmonary function tests (PFTs), and the absence of an obvious cause for pulmonary fibrosis, including environmental or occupational exposures, or collagen vascular diseases known to be associated with lung fibrosis. Radiologic HRCT scan findings for the diagnosis of a UIP pattern included the presence of bilateral, predominantly subpleural, basal reticular abnormalities and the absence of additional features considered incompatible with a diagnosis of IPF (possible UIP); a definite diagnosis required also the presence of honeycombing, a much more specific feature of a UIP pattern. The presence of upper or mid-lung predominance, peribronchovascular distribution, extensive ground glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s) was inconsistent with IPF (19, 20). Hystological findings for the diagnosis of a UIP pattern included marked fibrosis/architectural distortion ± honeycombing in a predominantly subpleural/paraseptal distribution, patchy involvement of lung parenchima by fibrosis and fibroblast foci; the presence of hyaline membranes, organizing pneumonia, granulomas, predominant airway centered changes, marked interstitial inflammatory cell infiltrate away from honeycombing was inconsistent with IPF (19, 20).

Familial IPF was defined as the presence of the above findings of IPF in two or more members of a biological family. Data were collected retrospectively from medical records and as diagnostic approaches have changed in the past several years, clinical diagnosis was subsequently confirmed by multidisciplinary consensus to avoid any biases contributed by the era they were collected; all radiological images and pathological slides were centrally reviewed.

Using these criteria, 27 families consisting of a total of 58 individuals (30 patients evaluated at our institution with a longitudinal follow-up and 28 additional family members evaluated outside of our institution) were identified. Patients have been inter-

viewed about their family history of IPF; to confirm the diagnosis of IPF in the relatives who were not followed-up in our unit, we obtained medical records of the assessments performed by the patients in other hospitals; open lung biopsy samples and radiographic studies were obtained. Family members in whom IPF was diagnosed outside of our centre were only accepted if the same established diagnostic criteria that were detailed above could be independently verified by review of the medical records, radiographs, or tissue samples. All sporadic case subjects had no affected first- second-degree family members.

All available baseline and follow-up data were recorded, including age, gender, symptoms, and smoking status as well as pulmonary function data, radiologic information and biopsy materials. Pulmonary function variables were expressed as percent predicted and included forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity of the lung for carbon monoxide (DLCO) using the single-breath technique. Time of initial diagnosis was defined as the date when IPF was first confirmed according to the above criteria and was defined by month and year, as recorded in the medical records (20). This study has been reviewed by the local ethic committee according to the Italian law (Prot. 450/2014 I.5/279).

Statistics

Clinical and physiologic data from the group of the 30 F-IPF patients with longitudinal follow-up information and from the 127 non-familiar IPF patients of our well characterized cohort of patients, were analyzed; initially descriptive statistical analyses were performed. Data were reported as the mean standard deviation (SD) for continuous variables and as percentages (%) for discrete variables. The familial and sporadic groups were compared using standard statistical approaches (^{2} test, Student t-test with two-tailed distribution).

The survival period was defined as the time interval from the date of the first evaluation to the date of death or the date of the last follow-up. Survival analysis was carried out with Kaplan-Meier method and the log-rank procedure was used to compare Kaplan Meier survival curves. In this analysis of our study, patients who were lost to follow-up were right-censored. In addition, patients with F-IPF were contrasted to patients with non familial IPF using a well-described database of individuals with IPF (log-rank to compare the survival between the two groups). A p value of $< 0,05$ was defined to represent a statistically significant difference.

Results

27 families consisting of a total of 58 individuals were identified (30 patients evaluated at our institution and 28 additional family members evaluated outside of our institution). All families were from Italian heritage and other ethnic origins were not represented. Affected siblings were the most common familial relationship identified in this cohort; from these 27 families, in 7 of them we found a parent–child relation. The ratio of men to women in this series was 0,75/1; 17 of these patients (56,7%) were current or former smokers, with a mean exposure of 34,5 pack-years; the mean age at first diagnosis of these 30 patients with familial IPF was 61,73 years (range 39 – 84 years) (Table 1). When we compared the age at onset within patients from different generations of the same family (parent-child), we found a lower age at onset in the younger generations (mean age 57,8 years versus 74,2 years) (Table 2).

The most common initial symptom in these 30 patients with FIPF was dyspnoea which has been described in 21 patients (70%); 17 patients complained of a persistent dry cough (56,7%), one patient had productive cough and fever as first symptoms (3,3%) and 2 patients were diagnosed during routine tests performed with no respiratory symptoms (Table 1). At the time of diagnosis, most patients had mild airway restriction; DLCO was reduced in 72,4 % of patients and lung volumes were reduced in 64,3 % of patients; 61,5% of patients demonstrated exercise oxygen desaturation (Table 3).

HRCT scanning was performed in all 30 patients. In 2 cases (6,67%), the reported findings were consistent with “definite”-UIP pattern, and included predominantly reticular and honeycomb patterns that were distributed preferentially in the peripheral and basilar regions of the lung; in 13 cases (43,33%) radiologic findings included bilateral, predominantly sub-pleural, basal reticular abnormalities without honeycomb (“possible”-UIP pattern); in 15 cases

Table 1. Comparison of demographic and clinical variables between familial and sporadic idiophatic pulmonary fibrosis

Variables	F-IPF n=30	Non F-IPF n=127	Significant difference(p)
AGE at diagnosis, yrs median (range)	61,73 (39-84)	64,17 (46-81)	0,15
GENDER (female F/male M)	16/12 (F 53%)	30/97 (F 24%)	0,00
CIGARETTE smoke			
current or former smokers	17 (56,7%)	93 (73,2%)	0,18
never smokers	13 (43,3%)	34 (26,8%)	
pack years, media	34,5	23,6	
CLINICAL PRESENTATION			
dyspnoea, n (%)	21 (70%)	93 (73,2%)	0,645
dry cough, n (%)	17 (56,7%)	65 (51,2%)	0,132
fatigue	0	4 (3,1%)	0,395
productive cough, n (%)	1 (3,3%)	0	0,068
fever, n (%)	1 (3,3%)	4 (3,1%)	0,959
other	0	7 (5,5%)	0,133
No symptoms, n (%)	2 (6,7%)	9 (7,1%)	0,94
HRCT, n of patients (%)			
definite UIP	2 (6,67%)	85 (66,94 %)	< 0,001
possible UIP	13 (43,33%)	26 (20,47 %)	< 0,001
inconsistent UIP	15 (50%)	16 (12,59 %)	< 0,001
LUNG CANCER, n of patients (%)	4 (13,3 %)	15 (11,8 %)	0,37
Squamous cell carcinoma	2 (50%)	6 (40%)	
Adenocarcinoma	1 (25%)	6 (40%)	
Small cell lung cancer	1 (25%)	3 (20%)	
CAUSES OF DEATH			
Acute exacerbation	3 (42,8%)	23 (43,4%)	< 0,98
Respiratory failure – IPF	1 (14,3%)	8 (15,1%)	< 0,95
Cancer	2 (28,6%)	9 (17%)	< 0,50
Lung transplantation complication	1 (14,3%)	2 (3,7%)	< 0,24
Other	0	6 (11,3%)	
Unknown	0	5 (9,4%)	

Table 2. Age at onset of pair of relatives from different generations with familial IPF.

	First generation (f-IPF)	Second generation (f-IPF)	Significance of difference (p)
Age at diagnosis (years)	74,2	57,8	0,001

(50%) radiologic HRCT scan findings were defined "inconsistent" with UIP pattern because of some upper or mid-lung predominance or peri-bronchovascular distribution, extensive ground glass abnormality, diffuse micronodules, profuse mosaic attenuation/air-trapping or consolidations (Table 1). 15 patients (50%) underwent surgical lung biopsies and a definite diagnosis was confirmed by multidisciplinary consensus in all patients.

Among the 30 patients who were managed longitudinally at the Morgagni – Pierantoni Hospital, the mean follow-up period was 24,7 months. Over this period, 7 patients died and 23 survived. Of those patients surviving at the time of analysis, 10 patients showed progressive deterioration, 2 underwent lung transplantation and 11 were relatively stable; 4 patients (13,3%) developed lung cancer during the follow-up period (squamous cell carcinoma 50%, ade-

Table 3. Comparison of pulmonary function tests (PFTs) at diagnosis between familial and sporadic groups.

Pulmonary Function Tests at Diagnosis					
LFTs	F-IPF patients with abnormal findings (FVC<80%p, TLCO<80%p, DLCO<80%p, SpO2<90%), N (%)	Mean +/- SD	Non F-IPF patients with abnormal findings, N (%)	Mean +/- SD	P
FVC,% p	12 (40%)	84,20 ± 20,37	65 (52,85%)	78,14 ± 17,29	0,099
TLC,% p	18 (64,3%)	72,64 ± 18,97	62 (78,48%)	70,99 ± 12,36	0,601
DLCO,% p	21 (72,4%)	51,09 ± 18,05	104 (95,41%)	51,51 ± 15,13	0,901
SpO2,%					
at rest	8 (30,8%)	95,85 ± 2,62	0	95,31 ± 1,83	0,25
on exercise	16 (61,5%)	90,54 ± 5,29	43 (55,12%)	88,95 ± 4,43	0,14

nocarcinoma 25%, small cell lung cancer 25%). No sustained benefit was reported in any of the treated patients.

Bronchoalveolar lavage (BAL) was performed in 22 patients (73 %); 12 patients (54,5 %) showed increased levels of neutrophils, while 4 patients (18,2 %) had increased numbers of lymphocytes. The mean values of the BAL fluid differential cell counts in these 22 patients were 14,8 % neutrophils and 11,9 % lymphocytes.

We compared the clinical phenotype of patients with familial IPF with patients with sporadic IPF, from a well-characterized database of patients with IPF from our institution (in total 127 patients). The ratio of men to women in this series was 3,23/1. 93 of these patients (73,2%) were current or former smokers, with a mean exposure of 23,6 pack-years; the mean age at first diagnosis of these 127 patients with sporadic IPF was 64,17 years (range 46 –81 years) (Table 1). The most common initial symptom was dyspnoea, which has been described in 93 patients (73,2%); 65 patients complained of a persistent dry cough (51,2%), 4 patients had fatigue (3,1%), 4 patients had fever, 7 patients had other symptoms as first manifestation like chest pain, joints pain or haemoptysis (5,5%), and 9 patients were diagnosed during routine tests performed without respiratory symptoms (7,1%) (Table 1). At the time of diagnosis, DLCO was reduced in 95,4% of patients and lung volumes were reduced in 52,3% of patients; 55,1 % of patients demonstrated exercise oxygen desaturation (Table 3).

HRCT scanning was performed in all 127 patients. In 85 cases (66,94 %), the reported findings were consistent with "definite"-UIP pattern; in 26 cases (20,47%) there were bilateral, predominantly sub-pleural, basal reticular abnormalities with no honeycomb ("possible"-UIP pattern); in 16 cases (12,59 %) radiologic HRCT scan findings were defined "inconsistent" with UIP (Table 1). 58 patients (45,7 %) underwent surgical lung biopsies and a definite diagnosis was confirmed by multidisciplinary consensus in all patients.

Among this cohort of 127 patients, the mean follow-up period was 39 months. Over this period, 53 patients died and 74 survived; among the surviving patients, 39 patients showed progressive deterioration, 8 underwent lung transplantation and 27 were relatively stable; 15 patients (11,8 %) developed lung cancer during the follow-up period (squamous cell carcinoma 40%, adenocarcinoma 40%, small cell lung cancer 20%).

BAL was performed in 85 patients (66,9 %); 60 patients (70,6 %) showed increased levels of neutrophils, while 8 patients (9,4 %) had increased numbers of lymphocytes. The mean values of the BAL fluid differential cell counts in these 85 patients were 28,2 % neutrophils and 9,1 % lymphocytes.

Comparing the familial and sporadic groups, there was no statistically significant difference in presenting symptoms (Table 1). Kaplan-Meier survival curves were generated and contrasted to compare survival outcomes between familial IPF and sporadic IPF (Figure 1). The mean survival time of familial IPF patients was 51,50 months from the time of diagnosis (95% confidence interval (CI), 38,67 to 64,33); in contrast, in this current study,

mean survival time of patients with sporadic IPF was 82,69 months (95% confidence (CI), 70,08 to 95,51). Although the survival of the f-IPF patients was very slightly shorter than those patients with sporadic IPF, this was not statistically significant. Thus, the overall clinical features and outcomes of familial IPF patients are quite similar to those of patients with non familial IPF.

Discussion

The main focus in this study was to define clinical features and survival time in a consecutive series of patients with familial IPF and to establish whether the phenomenon of anticipation could be observed.

Comparing the familial IPF and sporadic groups, there was no significant difference in presenting symptoms, the commonest presenting symptom being dyspnoea in both groups. However our cohort was much more enriched for females than the sporadic patient collection (Table 1); ratio of women to men was 16/12 in the familial IPF group (53% female) and 30/97 in the non familial IPF group (female 24%). These results were statistically significant (p<0,005) and were also observed in van Moorsel's study (3). Five earlier publications have described the clinical features of familial IPF or idiopathic interstitial pneumonia (IIP) cohorts (1, 9, 10, 21). Marshal et al. (1) identified 21 IIP families (containing 57 affected individuals); no attempt was made to determine the patients' IIP classification, but the UK cohort had a lower proportion of current or ever smokers (50% versus 80.3%). Lee et al. (9) published a collection of 15 familial IPF families with detailed clinical information on 27 patents, which were compared to 63 sporadic IPF patients; the main familial versus sporadic comparisons were age at diagnosis (59.4 years versus 63 years), and median survival which was similar between the 2 groups, at 2–3 years. Steele et al (21) recruited the largest familial cohort to date, 111 families with IIP containing 309 patients "definitely" or "probably affected" with IIP; the age range of diagnosis was wide (30.3–95.4 years). Van Moorsel et al (11) compared 22 unrelated familial IPF patients to 95 sporadic IPF cases; no familial versus sporadic differences were identified apart from younger diagnosis age in the familial group. The only other published IPF cohort from a founder population is Finnish (10); detailed clinical parameters were not published, but the only difference identified between the familial and sporadic groups was again mean age of diagnosis. In the current study, the age of onset was only slightly lower among the familial cases than in the sporadic cases of IPF (mean 61,17 years v 61,73 years, p= 0,146) (Table 1), however the familial IPF group had a wider range of age at diagnosis (39-84 years compared with 46-81 years in the sporadic group). Familial IPF has been suggested to occur at a younger age than IPF in non familial cases (7, 8); an early stage of asymptomatic lung disease has been previously reported by Marshall and co-workers (1), Hodgson and colleagues (10), and Bitterman and colleagues (4). More recently, Steele and associates reported that approximately 11% of subjects with familial IPF, without symptoms of pulmonary fibrosis had high-resolution computed tomography (HRCT) scan findings consistent with probable or definite interstitial pneumonia (21).

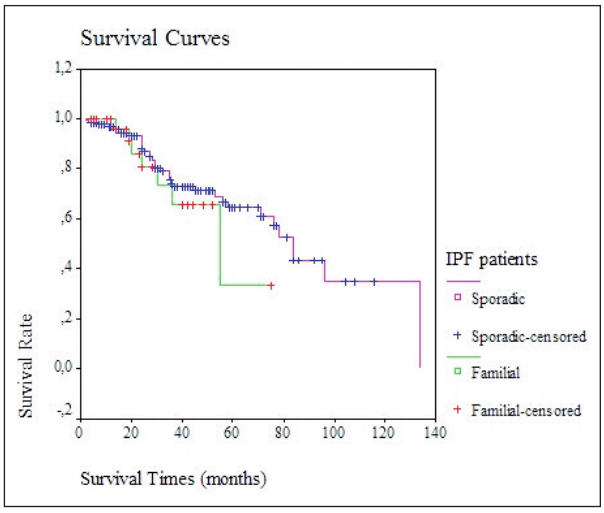

Fig. 1. Kaplan-Meier survival curves for familial IPF and sporadic IPF (mean survival time estimated by Kaplan-Meier analysis/Log Rank 51,50 months versus 82,69 months, p = 0,4701).

When we compared the age at onset within patients from different generations of the same family (parent-child), we found statistically significant lower age values at onset in the younger generations (mean age 57,8 years versus 74,2 years, p 0,001) (Table 2). The phenomenon characterized by the onset of the disease at an earlier age is known as "ge-

netic anticipation" and it is a widely known characteristic of many diseases with genetic inheritance. The molecular mechanisms underlying anticipation are largely unknown; it has been typically associated to trinucleotide repeat expansions in several genetic diseases: tandemly repeated trinucleotide sequences close to or within the disease-associated gene expand, changing from the marginally expanded premutant alleles associated with normal or subclinical phenotype, to large increases in copy numbers, and the fully expressed disease (12-15). Telomere shortening has been more recently described as another mechanism of anticipation, being associated with early onset and severity of disease in genetic disorders, such as dyskeratosis congenita (DC) (16, 17). In DC, anticipation occurs because of an accumulation of short telomerase across generations and highlights the role of telomere length and not only telomerase mutations, in determining disease onset and severity (16, 17). Premature aging can impair lung function by different ways: by interfering specifically with tissue repair mechanisms after damage, thus perturbing the correct crosstalk between mesenchymal and epithelial components; by inducing systemic and/or local alteration of the immune system, thus impairing the complex mechanisms of lung defense against infections; and by stimulating a local and/or systemic inflammatory condition (inflammaging). According to recently proposed pathogenic models in IPF, premature cellular senescence likely affects distinct progenitors cells (alveolar epithelial precursors), leading to stem cell exhaustion (18). Siblings that do not inherit a mutated TERC copy could not have early-onset of the clinical symptoms, even though they inherit shorter telomeres from the affected parent (22). Thus, individuals with AD-DC must both inherit shorter telomeres and be heterozygous with respect to TERC to show disease anticipation. In our series, the phenomenon of anticipation could be observed as comparing the age of initial diagnosis from pairs of patients of different generation belonging to the same family, age at diagnosis was younger in the subsequent generations.

Comparing the familial IPF and sporadic groups, the radiologic findings in our patients with familial IPF were not similar to those of patients with non familial IPF; honey combing occurred in a lower frequency than that reported for patients with non familial IPF and CT scan was more frequently inconsistent with a UIP-pattern (Table 1); this result is actually in line with previous and current literature (9, 23).

To assess the outcome of familial IPF patients, we compared data from patients in the current f-IPF series to data from a well-characterized database of patients with non familial IPF. Notably, although the survival of the familial IPF patients was very slightly shorter than those patients with sporadic IPF (51,50 months from the time of diagnosis versus 82,69 months), this was not statistically significant (Figure 1). Thus, the overall outcomes of familial IPF patients are quite similar to those of patients with non familial IPF. Only few studies have previously compared the survival of patients with familial IPF with a matched population of sporadic IPF patients. In the study published by Lee at al. in 2005, although the survival of the familial IPF patients was very slightly shorter than patients with sporadic IPF, this was not statistically significant (9). These results could suggest that patients in the two groups have the same disease behaviour. Analysing the causes of death in the two groups however, we did not find a significant difference between the two series: lung cancer was more frequent in the familial IPF group as a cause of death than in the sporadic group but this was not statistically significant and number of patients was too small to draw conclusions (Table 1). Furthermore, familial IPF patients developed more frequently squamous cell carcinoma (squamous cell carcinoma 50%, adenocarcinoma 25%, small cell lung cancer 25%) than sporadic IPF patients (squamous cell carcinoma 40%, adenocarcinoma 40%, small cell lung cancer 20%) (Table 4). Although our data show no association between the causes of death and the final prognosis, this could be an important supplemental information both in initial evaluation of disease status and in managing IPF patients (mostly regarding instrumental tests to perform during follow-up). A previous review of the available lung tissue samples from patients with familial IPF has consistently demonstrated the presence of superimposed features of diffuse alveolar damage and accelerated lung fibrosis UIP in some of the patients (24) and this could be explained by different pathogenetic mechanisms in these patients (25-28).

Regarding bronchoalveolar lavage (BAL), mean values of the BAL fluid differential cell counts in familial IPF patients and sporadic IPF patients re-

vealed respectively lower neutrophils values (14,8 % versus 28,2 %, p = 0,013) and higher lymphocytes values (11,9 % versus 9,1 %, p = 0,230). A previous study (4) reported evidence of lower respiratory tract inflammation in BAL fluid from half of clinically unaffected family members in three cohorts of familial lung fibrosis. However, it remains unclear whether this represents a universal finding among f-IPF families or whether asymptomatic lung inflammation predicts future lung fibrosis.

Our study had several limitations, mainly related to its retrospective and mono-centric nature. First, our department is a referral centre for IPF and one may argue that our results do not apply to all patients with Idiopathic Pulmonary Fibrosis. Secondly, the results on predictors of mortality must be interpreted with caution as the number of events was small. The role of anticipation is usually difficult to assess owing to clinical bias. This is because as soon as one family member is investigated for an inherited disease, the rest of the family are then subjected to increased clinical investigation. This observation could be due to ascertainment bias of subjects and lead-time bias, as a result of early detection of disease by extensive screening or surveillance programs in high risk families. Rare variant mutations in many different genes may be the basis for IPF and genetic anticipation might occur due to mutation in some specific genes, but not in others. Other lung diseases have been previously interpreted to have genetic anticipation that was artefactual (29). Penrose et al. listed several classes of bias of ascertaining disease that leads to the confusion (30). The first is initial discovery of a familiy by ascertainment of an offspring, which must lead to a time bias because the parent had to survive long enough to procreate; the second is the inherent age bias in any parent–child pair, whomever is the first case discovered. The third is failure to follow sibs long enough to discover age at disease onset of every potential case.

In summary, this study has characterized the clinic al features of a series of patients with familial IPF. F-IPF was indistinguishable from non F-IPF with respect to most clinical and physiologic findings; patients with F-IPF exhibited similar survival times when specifically compared to patients with non F-IPF. However the age of onset was only slightly lower among the familial cases than in the sporadic cases of IPF and the phenomenon of anticipation could be observed as, comparing the age of initial diagnosis from pairs of patients of different generation belonging to the same family, age at diagnosis was younger in the subsequent generations.

The careful screening and monitoring of family members of individuals with IPF will be necessary to determine the overall clinical behaviour and outcome. Furthermore we are now trying to verify (sequencing both TERC and TERT mutations and determining telomere length in blood sample of each patient) whether telomere shortening frequently occurs with successive generations in these families, suggesting that telomere shortening could be the mechanism to explain the phenomenon of age anticipation in this disease. Study of telomere length would be of relevance in the clinical surveillance and design of appropriate screening tests for patients with familial interstitial lung disease. Discovery of genetic mutations associated with disease and/or sensitive bioassays of early disease will facilitate the identification of individuals at high risk of development of asymptomatic ILD and will improve the ability to estimate the sensitivity and specificity of using HRCT scans for identification of early ILD.

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