A Familial History of Pulmonary Fibrosis in Patients with Chronic Hypersensitivity Pneumonitis

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Key Words

Familial idiopathic pulmonary fibrosis • Genetic susceptibility • Hypersensitivity pneumonitis

Abstract

Background: Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease induced by the inhalation of a variety of antigens. Patients with chronic HP often have a family history of pulmonary fibrosis. This strongly suggests that both genetic and environmental factors play an important role in the pathogenesis of chronic HP. **Objectives:** We aimed to investigate the epidemiology and clinical features of chronic HP patients with a family history of pulmonary fibrosis. **Methods:** We retrospectively reviewed the clinical information of 114 cases diagnosed with chronic HP with insidious onset between 1992 and 2009. **Results:** Twenty cases (17.5%) were identified as having a family history of pulmonary fibrosis. All of these patients had lived apart from their afflicted relatives for at least several decades. The familial cases were younger than the nonfamilial cases at onset (57.5 ± 9.6 vs. 64.0 ± 7.0 years old, $p = 0.008$). The predicted vital capacity percentage and partial pressure of oxygen in arterial blood gas were significantly higher in the familial cases. There were no differences between the 2 groups in gender,

smoking history, bronchoalveolar lavage fluid profile, radiologic findings or other clinical features. **Conclusions:** We found a familial clustering in patients with chronic HP. Various factors including genetic susceptibility to pulmonary fibrosis and environmental factors may contribute to the development of familial chronic HP.

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Introduction

We have experience of chronic hypersensitivity pneumonitis (HP) cases with a familial history of pulmonary fibrosis with variable causes. No systematic study to identify familial cases of chronic HP has been performed to date, and its true prevalence is unknown. A number of observations seem to support the contention that genetic factors influence the development of idiopathic pulmonary fibrosis [1–4]. It is difficult to differentiate the true inheritance of a disease from the mere clustering of cases within a family exposed to a common environmental factor in chronic HP. Yet the evidence to date suggests that both environmental and genetic factors play an important role in the etiology and pathogenesis of pulmonary fibrosis.

The clinical features of familial pulmonary fibrosis have not been fully defined because, along with radiologic and pathologic features and survival, they are indistinguishable from those of sporadic cases [5, 6]. However, there is evidence that the age of onset is younger [7–9]. Yang et al. [1] present 4 lines of evidence to support the notion that genetic factors influence the development of pulmonary fibrosis. First, the familial clustering of pulmonary fibrosis has been reported in monozygotic twins raised in different environments [10–12], and in family members separated at an early age [13]. Second, pulmonary fibrosis manifests pleiotropic presentations of genetic disorders including Hermansky-Pudlak syndrome [14] and familial surfactant protein C mutation [15]. Third, its development in asbestosis is variable among workers exposed to similar concentrations of dusts [16, 17]. Fourth, different strains of mice exhibit variable susceptibility to fibrogenic agents in a model of bleomycin-induced pulmonary fibrosis [18, 19].

The aim of this study was to investigate the epidemiology and the clinical features of chronic HP patients with a family history of pulmonary fibrosis.

Methods

Study Population

A retrospective review was conducted between 1992 and 2009 by analyzing the medical records of 183 patients diagnosed with chronic HP at the Tokyo Medical and Dental University Hospital. To minimize differences by clinical subtype, the population enrolled was confined to patients with chronic HP with insidious onset induced by bird-related antigens ($n = 114$). The diagnostic criteria for chronic HP comprised 3 or more of the following: (1) a recurrence of HP symptoms triggered by an environmental stimulus or laboratory-controlled inhalation of the antigen, (2) antibodies and/or lymphocyte proliferation to the antigen, (3) evidence of pulmonary fibrosis with or without granulomas, (4) honeycombing evident on CT scans (5) progressive deterioration of a restrictive impairment in pulmonary function over the course of 1 year and (6) persistence of respiratory symptoms associated with HP for more than 6 months [20–22]. Patients with 1st-degree relatives with a history of pulmonary fibrosis were defined as the familial cases. Demographic characteristics, laboratory findings, pulmonary function tests, bronchoalveolar lavage (BAL) profiles, high-resolution computed tomography (HRCT), histology and prognosis were examined in both familial and nonfamilial cases. The age of onset was defined as the earliest date of the first abnormality on chest X-ray, HRCT scan or lung biopsy. The study was conducted in conformity with the Declaration of Helsinki and was approved by the Internal Review Board at Tokyo Medical and Dental University.

Bronchoalveolar Lavage

BAL was performed as previously described using three 50 ml aliquots of sterile 0.9% saline [23]. The cellular composition of the

BAL fluid was determined using a cytopspin smear with Wright's stain by counting 200 cells. Lymphocyte phenotypes were assessed by flow cytometer with monoclonal antibodies for CD4 and CD8.

High-Resolution Computed Tomography Scoring

HRCT scans were evaluated independently by 5 experienced respiratory physicians (Drs. Yasunari Miyazaki, Masato Kishi, Torahiko Jinta, Haruhiko Furusawa and Tsukasa Okamoto) who had no knowledge of the clinical histories. The evaluators assigned a ground-glass opacity score and a score for fibrosis based on the reticular opacity. The scoring system used for the evaluations has been described by Kazerooni et al. [24]. Each lobe of the lung was scored on a scale of 0–5. The averages of the scores for each lobe assigned by the 5 evaluators were used for the analysis.

Pathological Assessment

Lung tissues were obtained from 46 cases by video-assisted thoracoscopic surgery. Histological patterns were interpreted by 2 pulmonary pathology specialists (Drs. Tamiko Takemura and Takumi Akashi) who had no knowledge of the patients' clinical information. All specimens were pathologically compatible with chronic HP described previously [25]. The patterns were classified into the usual interstitial pneumonia (UIP) pattern, the fibrotic nonspecific interstitial pneumonia (fNSIP) pattern and the cellular nonspecific interstitial pneumonia (cNSIP)/organizing pneumonia (OP) pattern, according to the International Classification of Idiopathic Interstitial Pneumonias proposed by the 2002 ATS/ERS statement [26].

Immunological Test

Antibodies in sera and BAL fluids to pigeon-dropping extract (PDE) were measured by an enzyme-linked immunosorbent assay (ELISA) [27]. Experiments showed positive data of ≥ 3.0 for IgG or ≥ 1.0 for IgA (data not shown).

Antigen-induced lymphocyte proliferation was performed as previously reported [27]. Peripheral or bronchoalveolar lymphocytes (2×10^5 cells) were cultured in quadruplicate with a 1:100 dilution of pigeon sera in 96-well flat-bottom plates. The plates were incubated for 5 days at 37°C in a 5% CO₂ incubator with ³H-thymidine for the last 16 h of culture. The results were expressed as a stimulation index, which is the geometric mean counts per minute of stimulated cultures with pigeon sera divided by the geometric mean counts per minute of unstimulated cultures as control. Experiments showed that a positive stimulation index was ≥ 1.8 (data not shown).

Criteria for Acute Exacerbations

The criteria for acute exacerbation (AE) were described previously [28]. These criteria included: (1) aggravation of dyspnea within 1 month, (2) hypoxemia with an arterial oxygen tension/inspired oxygen tension ratio of <225 , (3) newly developing pulmonary infiltrates on chest radiographs and (4) the absence of any apparent infection or heart disease.

Statistical Analysis

Data were analyzed using a statistical software package (SPSS Statistics 17.0; Chicago, Ill., USA) and described as medians $\pm$ quartile deviations (QD). The 2 groups were compared using the Mann-Whitney U test. Comparisons between groups were per-

Table 1. Patient information of familial and nonfamilial cases

	Familial	Nonfamilial	p value
Male/female	15/5	62/32	0.6
Age of onset ^a	57.5 ± 9.6	64.0 ± 7.0	0.008
Smoking history (never/ex/current)	6/14/0	37/42/15	0.057
Pack-year	18.8 ± 15.0	20.5 ± 22.5	0.649
Clubbed finger (+/-)	7/13	47/42	0.216

Values are given as median ± QD or a number.

^a Age of onset is defined as the earliest date among the date of detection of abnormality on chest X-ray.

formed using the χ^2 or the Fisher exact test for categorical variables. The following clinical parameters were analyzed to identify the potential association with age of onset by multivariate analysis using the Cox proportional hazard regression model: familial history, gender, smoking history, clubbed finger, Krebs von den Lungen 6 (KL-6), C-reactive protein (CRP), predicted vital capacity percentage (% VC), partial pressure of oxygen in arterial blood (PaO₂) and the percentage of lymphocytes in BAL fluid. All statistical comparisons were 2-sided, and p values of less than 0.05 were considered significant. The cumulative incidence ratio and cumulative survival probabilities were estimated by the Kaplan-Meier method. The log-rank test was used to compare the incidence of pulmonary fibrosis to the survival time or age of onset in both the familial and nonfamilial cases of chronic HP.

Results

Patient Characteristics

Among the 114 cases of insidious chronic HP, 20 (17.5%) were identified as familial cases according to the criteria described in the Methods section. Regarding the relationship between the index cases and the family members with pulmonary fibrosis, 9 index cases had parent-child relationships, 9 had sibling relationships and 2 had both parent-child relationships and sibling relationships. Two patients were from a family with many pulmonary fibrosis cases (online supplementary fig. S1; for all online supplementary material, see www.karger.com/doi/10.1159/000338123). All of the familial patients had lived apart from their afflicted relatives for at least several decades. No patient had any known history of inhaling asbestos or dusts. According to the self-reports from patients, the afflicted relatives had been diagnosed with the following types of pulmonary fibrosis: 17 idiopathic interstitial pneumonias, 12 cases of idiopathic pulmonary fibrosis, 3 cases associated with rheu-

Fig. 1. Cumulative incidence probabilities between familial and nonfamilial cases were compared using the Kaplan-Meier method. The age of onset in familial cases was significantly younger than that in nonfamilial cases using the log-rank test (median age: familial 57.5 vs. nonfamilial 64.0 years, $p = 0.0015$).

matoid arthritis, 1 chronic HP and 1 case associated with scleroderma (online suppl. table S1). Although they had all been diagnosed in the tertiary referral hospitals, the clinical information of afflicted relatives was limited, because some people were very old, dead or had gone to other hospitals.

The patient characteristics of the familial and nonfamilial cases are shown in table 1. There were about twice as many male cases of chronic HP than female, in both the familial group and nonfamilial group. In the comparison of the median age of onset, the familial cases turned out to have a median age about 6.5 years younger than the nonfamilial cases (57.5 ± 9.6 vs. 64.0 ± 7.0 years old, respectively; $p = 0.008$). The incidence of chronic HP by age was estimated using a Kaplan-Meier method (fig. 1). The onset came earlier in the familial group than in the nonfamilial group using a log-rank test ($p = 0.0015$). The major symptoms at diagnosis of chronic HP were cough and dyspnea. There was no difference between the 2 groups in the frequency of these symptoms.

Laboratory Findings, Pulmonary Function Test and BAL

Table 2 shows laboratory findings and the results of pulmonary function tests. Familial cases of % VC and PaO₂ were significantly higher than in nonfamilial cases (% VC: 85.8 vs. 73.6%, $p = 0.025$; PaO₂: 93.5 vs. 80.0 mm Hg, $p = 0.014$, respectively). There were no significant dif-

Table 2. Laboratory data and pulmonary function test

	Familial		Nonfamilial		p value
	median $\pm$ QD	n	median $\pm$ QD	n	
CRP, mg/dl	0.10 $\pm$ 0.11	17	0.28 $\pm$ 0.20	68	0.060
LDH, IU/l	225 $\pm$ 28	17	256 $\pm$ 43	67	0.164
KL-6, U/ml	1,215 $\pm$ 767	18	1,500 $\pm$ 807	77	0.406
SP-D, ng/ml	267 $\pm$ 122	15	228 $\pm$ 146	70	0.576
% VC	85.8 $\pm$ 8.9	19	73.6 $\pm$ 14.8	84	0.025
% DLco	63.1 $\pm$ 13.0	16	53.8 $\pm$ 14.3	69	0.109
% DLco/VA	72.4 $\pm$ 11.9	13	67.4 $\pm$ 12.5	67	0.629
PaO ₂ , mm Hg	93.5 $\pm$ 8.3	12	80.0 $\pm$ 7.4	77	0.014

% DLco = Diffusing lung capacity for carbon monoxide percentage predicted; % DLco/VA = diffusing lung capacity for carbon monoxide per alveolar volume; SP-D = surfactant protein D.

Table 3. BAL fluid profiles

	Familial		Nonfamilial		p value
	median $\pm$ QD	n	median $\pm$ QD	n	
Cell counts, $\times 10^5$ /ml	3.56 $\pm$ 1.17	13	3.75 $\pm$ 1.30	70	0.172
Macrophages, %	80.0 $\pm$ 5.8	17	78.6 $\pm$ 11.9	73	0.335
Lymphocytes, %	9.7 $\pm$ 5.8	17	14.6 $\pm$ 9.4	74	0.088
Neutrophils, %	2.3 $\pm$ 1.4	17	2.6 $\pm$ 2.4	74	0.850
Eosinophils, %	0.9 $\pm$ 0.9	17	1.0 $\pm$ 1.0	73	0.736
CD4:CD8	1.8 $\pm$ 1.1	10	2.4 $\pm$ 2.3	61	0.372

ferences in laboratory findings or in BAL fluid analysis (table 3).

The following clinical parameters were analyzed by the Cox proportional hazard regression model to identify which variables were associated with the age of onset: familial history, gender, smoking history, clubbed finger, KL-6, CRP, % VC, PaO₂, and the percentage of lymphocytes in BAL fluid. A familial history of pulmonary fibrosis proved to be significantly and independently associated with the age of onset ($p = 0.029$), with a hazard ratio of 2.442 [95% confidence interval (CI) 1.094–5.448] (table 4).

HRCT, Pathological Assessment and Immunological Findings

There were no significant differences in HRCT findings (table 5). Six (30%) familial cases and 40 (43%) nonfamilial cases underwent surgical lung biopsies. All 6 of

Table 4. Multivariate analysis evaluating age of onset for clinical parameters

	Partial regression coefficient	p value	Hazard ratio	95% CI
Familial history	0.893	0.029	2.442	1.094–5.448
Gender	−0.238	0.597	1.268	0.525–3.062
Smoking history	−0.218	0.626	0.804	0.334–1.938
Clubbed finger	−0.391	0.195	0.676	0.375–1.221
KL-6	0	0.169	1.000	1.000–1.000
CRP	−0.247	0.508	0.781	0.376–1.624
% VC	0	0.967	1.000	0.983–1.018
PaO ₂	0.003	0.842	1.003	0.975–1.031
Lymphocytes % of BAL	−0.008	0.399	0.992	0.975–1.010

Cox's proportional hazard model was employed to evaluate the relation of age of onset to clinical parameters, including familial history, gender, smoking history, clubbed finger, KL-6, CRP, % VC, PaO₂ and the percentage of lymphocytes in BAL fluid.

Table 5. Radiological analysis of HRCT

	Familial (n = 17)	Nonfamilial (n = 68)	p value
Fibrosis score	1.8 $\pm$ 0.7	2.1 $\pm$ 0.5	0.448
Ground-glass score	2.0 $\pm$ 0.4	2.2 $\pm$ 0.4	0.077

Values are given as median $\pm$ QD.

The outlines of the scoring system used for the evaluation have been described previously [24].

the biopsied familial cases showed a UIP pattern, while the 40 biopsied nonfamilial cases showed 21 UIP patterns (52.5%), 17 fNSIP patterns, and 1 cNSIP pattern ($p = 0.039$) (table 6). There was no difference in the positive rate of the specific antibodies or in the lymphocyte proliferation test (table 7).

Prognosis and Acute Exacerbations of Chronic HP

There was no significant difference in the survival analysis (familial cases vs. nonfamilial cases: median age of 75 vs. 79 years old, $p = 0.093$), and the prognoses from onset were similar ($p = 0.812$) (fig. 2). Out of 33 fatal cases (6 familial and 27 nonfamilial), 13 (2 familial and 11 nonfamilial) presented with AE. The frequency of AE did not differ between the 2 groups ($p = 1.000$). Other causes of death included chronic respiratory failure ($n = 6$), bacterial pneumonia ($n = 3$), lung cancer ($n = 2$),

Table 6. Histologic analysis in familial and nonfamilial cases

Pathological pattern	Familial		Nonfamilial	
	n	%	n	%
UIP	6	100	21	52.5
fNSIP	0	0	17	42.5
cNSIP	0	0	1	2.5
OP	0	0	0	0
Not available	0	0	1	2.5

Table 7. Immunological findings

	Familial		Nonfamilial		p value
	+/-	positive, %	+/-	positive, %	
Anti-PDE antibodies	16/4	80	70/14	83	0.746
Lymphocyte proliferation test	7/11	39	27/41	40	1.000

Antibodies in sera and BAL fluid to PDE were measured by enzyme-linked immunosorbent assay; cutoff point for IgG >0.3 and for IgA >0.1.

In vitro proliferation of peripheral and bronchoalveolar lymphocytes to avian sera; cutoff point >1.8.

pneumothorax (n = 1), myocardial infarction (n = 1), sepsis (n = 1), pharyngeal cancer (n = 1) and unknown causes (n = 5).

Discussion

We identified familial clustering in 17.5% of the cases of chronic HP with insidious onset, even though all of the familial cases had lived apart from their afflicted relatives for at least several decades. In addition, we identified a pair of monozygotic twins within the familial population. We also found that the age of onset was significantly younger in the familial chronic HP group than in the nonfamilial group, and that the age of onset was independently associated with a familial history of pulmonary fibrosis. These findings suggest that various factors including genetic and environmental may play an important role in the development of the chronic HP.

The prevalence of familial chronic HP in this study was 17.5%, whereas previous reports showed prevalence

Fig. 2. Cumulative survival probabilities between familial and nonfamilial cases were compared using the Kaplan-Meier method. The survival time of familial cases tended to be shorter than that of nonfamilial cases.

of familial idiopathic pulmonary fibrosis ranging from only 0.5 to 3.7% [7, 9]. This disparity in prevalence may stem from a susceptibility to environmental antigens in some of the patients or a referral bias at a tertiary center. There is some variability in the development of pulmonary fibrosis among workers exposed to similar concentrations of dust in asbestosis [16, 17]. On this basis, we assume that both environmental and genetic factors contribute to the higher prevalence of familial chronic HP compared to familial pulmonary fibrosis. While all of the familial patients had lived apart from their afflicted relatives for at least several decades, we noted that the antigen sensitization could have occurred in childhood and the relatives could have been exposed to the same antigens by coincidence as adults.

The role of genetic susceptibility in chronic HP is still undefined. In studies on acute HP, researchers have investigated the genetic background by human leukocyte antigen typing [29], tumor necrosis factor alpha [30], and tissue inhibitors of metalloproteinases [31]. There are also the potential candidate genes influencing the immunological response to injury and modulate collagen metabolism in the lung. In one study on chronic HP, Diaz de Leon et al. [32] identified 2 chronic HP patients as *TERT* mutation carriers; this suggests that patients with various forms of interstitial pneumonia such as HP might have gene susceptibility to pulmonary fibrosis. We can improve our understanding of the pathogenic mechanisms of fibrosis by identifying which genes confer a suscepti-

bility to pulmonary fibrosis in familial cases of chronic HP. In this study we identified one large kindred. We are currently investigating the genetic susceptibility of pulmonary fibrosis using a genome-wide linkage analysis of this family, as shown by Wang et al. [33].

The age of onset of chronic HP was younger in familial cases than in nonfamilial cases. In the study by Marshall et al. [7], the patients with familial idiopathic pulmonary fibrosis were younger at diagnosis but were otherwise indistinguishable from the nonfamilial cases. The younger onset of familial cases in this study might be associated with genetic susceptibility. Moreover, the familial cases tended to have a poor survival outcome than nonfamilial cases. Increasing the sample size might determine that the familial history of pulmonary fibrosis is a poor prognostic factor in chronic HP. Nevertheless, a potential lead time bias cannot be ruled out, because subjects having a parent or sibling with pulmonary fibrosis should undergo earlier screening.

All 6 of the familial cases manifested a UIP pattern, whereas the nonfamilial cases manifested 21 UIP patterns (52.5%), 17 fNSIP patterns and 1 cNSIP pattern (table 6). In chronic HP, we found several clinical differences between cases with a UIP pattern and an fNSIP pattern. Ohtani et al. [34] showed that the percentage of lymphocytes in BAL fluid was lower in patients with a UIP pattern than in patients with an fNSIP pattern. In this study, however, the percentage of lymphocytes in BAL fluid tended to be lower in familial cases than in nonfamilial cases. This finding might derive from the higher proportion with a UIP pattern in our familial cases. In a previous study on chronic bird fancier's lung, a UIP pattern in histology at baseline appeared to be a stronger risk factor for acute exacerbation than an fNSIP pattern or a cNSIP pattern [28], but in our study we found no difference in the incidence of AE between the 2 groups.

There were several limitations in this study. First, it was retrospective; we will need to conduct a prospective study to certify the results. Second, the sample size, particularly of the familial group, was too small to generalize our results. Third, there was a significant referral bias, as our hospital is a clinical center for chronic HP. Finally, the lack of any formalized standard definition for HP complicates the diagnosis [35]. We relied on immunological and histological findings to diagnose chronic HP, as patients with chronic HP rarely have classic systematic symptoms such as fever with shivering or aching muscles.

In conclusion, we found a familial clustering in patients with chronic HP, even though the disease is uncommon. Various factors including genetic susceptibility to pulmonary fibrosis and the environment may contribute to the development of familial chronic HP.

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