Idiopathic Pulmonary Fibrosis in Monozygotic Twins*

The Importance of Genetic Predisposition


Idiopathic pulmonary fibrosis (IPF) proved by lung biopsy occurred in a pair of monozygotic twin brothers who had lived apart for many years. Histopathology of the two cases was almost identical. The purpose of this report is to substantiate the role of genetic factors in the development of IPF.

The development of similar disease in monozygotic twins suggests that inherited susceptibility is an implicit risk factor. Both environmental factors and inherited susceptibility are considered to play major roles in the development of certain disorders, such as diabetes mellitus,1 systemic lupus erythematosus,2 and tuberculosis.3

Interstitial pulmonary fibrosis is a relatively common disease which has been associated with a variety of etiologic factors, such as severe pulmonary infection, irritant dusts, collagen vascular disorders, syndromes of hypersensitivity pneumonitis, and chemotherapeutic agents. In many instances, no associated cause can be identified, and the term idiopathic pulmonary fibrosis seems appropriate for this group of patients.4 (Other synonyms, some of which may depend on the pathologic stage of the disease, include cryptogenic fibrosing alveolitis, desquamative interstitial pneumonia, usual interstitial pneumonia, idiopathic interstitial pneumonia, and Hamman-Rich syndrome.)

We report the occurrence of biopsy-proven idiopathic pulmonary fibrosis in a pair of monozygotic twins who developed symptoms concurrently. They had not lived together since childhood. Both also had diabetes mellitus. Twin 1 developed the disease while on treatment with steroids; and twin 2, who had chemical diabetes mellitus, became symptomatic shortly after therapy. This report suggests that genetic factors may play a major role in the development of idiopathic pulmonary fibrosis.

CASE REPORTS

CASE 1

A 51-year-old male nonsmoker (twin 1) was referred to the hospital for evaluation of progressive interstitial pulmonary disease. He has been in good health, with the exception of mild hypertension treated with hydrochlorothiazide. At the age of 48 years, during a routine physical examination, the patient was told that he had an abnormal chest roentgenogram. Since that time, he has had a nonproductive cough in the morning and shortness of breath with exercise. The patient denied any pain in the chest, hemoptysis, arthritic symptoms, previous history of thoracic infections, or the taking of any other medicine known to be associated with pulmonary fibrosis. His occupational history was entirely benign. The patient has been an electrical utility worker but was never exposed to any chemicals, including asbestos or beryllium. His family history revealed that one twin brother (they had one placenta at birth) also had a pulmonary disorder.

The patient's blood pressure was 160/110 mm Hg. There were bilateral end-inspiratory rales. There was no evidence of cardiac, renal, musculoskeletal, or cutaneous abnormalities. The patient's blood group was A+. The results of the following laboratory tests were normal: tests of renal and hepatic function; complete blood cell count; total eosinophil count; sedimentation rate; antinuclear antibody, rheumatoid factor; serum protein agarose electrophoresis; and immunoelectrophoresis. The level of glucose in the blood was 82 mg/100 ml. No circulating immune complexes were detected in the serum (Raji-cell technique).5 Cutaneous tests for tuberculosis and fungi were negative, but the test for mumps was positive.

The chest roentgenogram revealed a bibasilar reticulonodular pattern. The mediastinum, pleura, and heart appeared normal. A lung scan with radioactive 67gallium was normal. Tests of pulmonary function (Table 1) revealed a mild restrictive defect, with reduction in pulmonary volumes and impairment of gas exchange, but a normal maximum expiratory peak flow rate and a normal ratio of the forced expiratory volume in one second (FEV1) over the forced vital capacity (FVC) expressed as a percentage (FEV1/FVC%).

A transbronchial biopsy of the lung was obtained. Cultures of the biopsy for mycobacteria and fungi were negative. Therapy with prednisone (60 mg daily) was administered,
Table 1—Pulmonary Function*

<table>
<thead>
<tr>
<th>Data</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity, L</td>
<td>5.3 (74)</td>
<td>5.1 (68)</td>
</tr>
<tr>
<td>Vital capacity, L</td>
<td>3.9 (72)</td>
<td>3.9 (78)</td>
</tr>
<tr>
<td>Residual volume, L</td>
<td>1.4 (62)</td>
<td>1.2 (48)</td>
</tr>
<tr>
<td>Functional residual capacity, L</td>
<td>2.5 (82)</td>
<td>2.5 (60)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>3.1 (79)</td>
<td>3.0 (78)</td>
</tr>
<tr>
<td>FEV₁/FVC %</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>Arterial oxygen pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>Exercise**</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Arterial carbon dioxide tension, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Exercise**</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Steady-state diffusing capacity for carbon monoxide, ml/min/mm Hg</td>
<td>10 (45)</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent predicted value (from Kory and co-workers[16]).
**Exercise was performed by non-steady-state technique.

with some improvement in pulmonary function. The patient developed symptomatic diabetes mellitus while receiving steroids, necessitating administration of insulin.

Case 2

A 50-year-old chemistry teacher who was the monozygotic twin of case 1 was admitted to the hospital in March 1977, after six weeks of a nonproductive cough and gradually increasing exertional dyspnea which did not improve after three weeks of treatment with tetracycline. The patient (twin 2) had had poliomyelitis at the age of seven years, without any residual neurologic or musculoskeletal deficits. He had been told two years before that he had mild diabetes and had been advised to lose weight. The patient had had an appendectomy and vasectomy. He had smoked a pipe for many years, plus one to three cigarettes per day, but had stopped smoking three months prior to admission.

On physical examination the respiratory rate was 26/min; the patient had bibasilar rales and early clubbing of the fingers. No other abnormalities were noted. His blood group was A+. The level of hemoglobin was 17.1 gm/100 ml; the white blood cell count was 11,000/cu mm, with a normal differential cell count; and the level of glucose in the blood was 160 mg/100 ml. The results of the following tests were normal: tests of renal and hepatic function; electrocardiogram; serum protein agarose electrophoresis; VDRL test; direct and indirect Coombs’ test; rheumatoid factor; and antinuclear antibody. Serologic tests for Histoplasma, Blastomyces, Cryptococcus, Candida, Aspergillus, and Coccidioides were all negative. Serologic tests for influenza, Eaton agent, adenovirus, reovirus, respiratory syncitial virus, Chlamydia, Echovirus, and Coxsackie B virus were negative. No circulating immune complexes were detected in the serum.

Tests of pulmonary function (Table 1) showed a moderately severe restrictive defect, with evidence of impaired gas exchange. The chest x-ray film demonstrated a reticulonodular pattern at the bases, without cardiac, mediastinal, or pleural disease. The patient underwent an open lung biopsy.

*Figures 1 and 2.*

Figure 1. Lung biopsy of twin 1. Pulmonary architecture is distorted by marked interstitial fibrosis. Inflammation is slight. Small pulmonary artery (at left) has marked fibrous mural thickening (hematoxylin-eosin, original magnification × 160).

Cultures of the specimen from biopsy grew no mycobacteria or fungi.

After one week of therapy with prednisone (60 mg daily), the patient noted the gradual development of polydipsia, polyuria, and polyphagia. The level of glucose in his blood was 434 mg/100 ml. The patient was treated with insulin. Over the next four months, he noted some lessening of his cough and dyspnea and was able to reduce his dosage of insulin and to taper his therapy with prednisone to 15 mg/day. Pulmonary function tests showed mild improvement.

Histopathologic Findings

The morphologic findings in the transbronchial biopsy obtained from twin 1 (case 1) and the open lung biopsy of twin 2 (case 2), allowing for differences in the size of the sample, were practically identical and will be described together (Fig 1 and 2). The pulmonary architecture was diffusely distorted by interstitial inflammation and fibrosis. Interalveolar septa measured up to 50μ in thickness. Only a rare interalveolar septum was of normal width. The inflam-
Table 2—HL-A Typing in the Family

<table>
<thead>
<tr>
<th>Relation</th>
<th>A Locus</th>
<th>B Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin 1</td>
<td>A2A1W11</td>
<td>B7B41</td>
</tr>
<tr>
<td>Twin 2</td>
<td>A2A1W11</td>
<td>B7B41</td>
</tr>
<tr>
<td>Sister</td>
<td>A2</td>
<td>B1</td>
</tr>
<tr>
<td>Daughter of twin 1</td>
<td>A2A1</td>
<td>B7BW35</td>
</tr>
<tr>
<td>Son of twin 1</td>
<td>A2A1</td>
<td>B7B41</td>
</tr>
<tr>
<td>Son of twin 2</td>
<td>A2A1</td>
<td>B7B41</td>
</tr>
<tr>
<td>Mother of twins</td>
<td>A2A11</td>
<td>B7BW35</td>
</tr>
</tbody>
</table>

matory infiltrate was composed of lymphocytes and rare macrophages only. The excessive interstitial collagen was dense and mature. Hyperplastic type-2 pneumocytes lined the air spaces. The alveoli did not contain inflammatory cells. Polarization revealed no birefringent foreign material. Pulmonary arteries in twin 1 had marked fibrous mural thickening involving both the intima and media. No granulomas were present.

Survey of the Family

None of the first-degree relatives of the twins (Table 2) examined had any evidence of pulmonary disease. There was no history of rheumatoid arthritis, Schönlein-Henoch purpura, Raynaud’s disease, albinism, or von Recklinghausen’s neurofibromatosis. The father of the twins had died of coronary heart disease, with no evidence of pulmonary disease. The HL-A antigenic phenotypes of the twins and the first-degree relatives (Table 2) were different from those initially reported in idiopathic pulmonary fibrosis.

Discussion

Pulmonary fibrosis, once a rare entity known as the Hamman-Rich syndrome, is now a frequently recognized and well-described pathophysiologic entity. It is probably not a single disease, in that many different pathologic processes can lead to pulmonary fibrosis. In the majority of the cases, the cause remains unknown, and the disease is best referred to as idiopathic pulmonary fibrosis. (Twin 1 was treated with hydrochlorothiazide, but it is unlikely that this was etiologically related to pulmonary fibrosis, since the other twin was not receiving the drug.) There are several reports which indicate that genetic predisposition plays an important role in the development of idiopathic pulmonary fibrosis.

The association of idiopathic pulmonary fibrosis with certain autosomally transmitted diseases suggests that such fibrosis may also be transmitted genetically. The initial cases of idiopathic pulmonary fibrosis associated with von Recklinghausen’s neurofibromatosis were followed by the systematic report of Massaro and Katz, who reviewed 88 cases of von Recklinghausen’s disease and found 20 patients with abnormal chest roentgenograms. Pulmonary tissue was available from six such patients, all of which showed evidence of alveolitis and interstitial fibrosis. The roentgenographic changes in the 20 patients included diffuse mottled infiltrate, diffuse linearity, and bullae. It therefore appears that the incidence of idiopathic pulmonary fibrosis is increased in patients with neurofibromatosis. Because neurofibromatosis is transmitted genetically as an autosomal dominant, it is conceivable that idiopathic pulmonary fibrosis has a genetic predisposition as well.

A more important reason suggesting genetic predisposition to the development of idiopathic pulmonary fibrosis is the reported familial clustering of patients with this disease. The following two specific aspects of familial idiopathic pulmonary fibrosis deserve to be emphasized: (1) familial idiopathic pulmonary fibrosis transmitted as a mendelian autosomal dominant; and (2) the occurrence of idiopathic pulmonary fibrosis in monozygotic twins.

The term, familial fibrocystic pulmonary dysplasia, has been used to refer specifically to the familial form of idiopathic pulmonary fibrosis. In a review of the literature, Donohue et al found 23 familial cases in 87 cases of the Hamman-Rich syndrome. Adelman et al added six more cases of familial fibrocystic dysplasia and confirmed the pattern of autosomal dominant transmission.

We have found one definite and one probable but not proven report of idiopathic pulmonary fibrosis in two other pairs of identical twins. The first report was by Peabody et al, who studied two sisters, the first of whom became symptomatic at the age of 44 years and died within three years due to respiratory failure. Postmortem examination revealed pulmonary fibrosis. The other twin, who had lived away from her sister, became symptomatic at the age of 43 years and died seven years later. More recently, Solliday et al reported five patients with idiopathic pulmonary fibrosis in three generations of one family, including a pair of twin brothers. They both became symptomatic in their early 20s, and both showed evidence of a restrictive defect on studies of pulmonary function. The diagnosis was proven in one of the twins by open lung biopsy.

Our patients became symptomatic in their sixth decade of life, and both proved to have interstitial fibrosis by lung biopsy. They had lived far apart since 15 years of age and had no known identifiable cause of pulmonary fibrosis.

The occurrence of diabetes mellitus in our two patients is in accord with the recent findings of diabetes mellitus in both identical twins after the age of 40 years, once a co-twin has been affected. This finding further emphasizes the importance of...
genetically determined disease, which in this instance was brought about by therapy with steroids.

The initial report of increased association of certain HL-A antigens with idiopathic pulmonary fibrosis has not been substantiated, and the distribution of HL-A antigen in our patients and their immediate family (Table 2) is in accord with the latter finding.

The importance of the finding of well-documented idiopathic pulmonary fibrosis in these identical twins lies in the possible role that genetic predisposition may play in the pathogenesis of this syndrome. A model could be proposed in which both environmental and genetic factors play important roles in the genesis of pulmonary fibrosis. The contribution of these two factors in the pathogenesis of many other diseases has been emphasized in the literature. Certain environmental factors can lead to the development of pulmonary fibrosis, probably regardless of genetic predisposition. Asbestos and beryllium, drugs such as furodantin and bleomycin, and a variety of infections leading to pulmonary fibrosis are some examples of environmental inducers. Admittedly, further genetic studies, such as HL-A typing, are necessary to exclude the possibility of genetic predisposition even in these cases, particularly since only some of the exposed population will subsequently be the victims of pulmonary fibrosis. On the other hand, the occurrence of idiopathic pulmonary fibrosis in identical twins who have lived far apart for many years emphasizes the importance of genetic predisposition. It is conceivable that with strong genetic predisposition, trivial pulmonary insults, such as a viral infection, could lead to the development of pulmonary fibrosis. Clinical viral-like infections of the respiratory tract frequently precede the development of pulmonary fibrosis, and 40 percent of these patients relate that their disease began after a viral syndrome accompanied by thoracic symptoms. It is conceivable that associated injury to pulmonary tissue leads to structural alteration of previously self-recognized antigens or exposure to new antigens. It has been shown that more than 95 percent of the patients with idiopathic pulmonary fibrosis have circulating lymphocytes that produce lymphokines when exposed to type-1 collagen, a structural component of the pulmonary interstitium. In a "genetically predisposed person," subsequent immunologic responses to the new antigen can lead to further injury to tissue and eventual pulmonary fibrosis.

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REFERENCES