Jpn. J. Human Genet. **28**, 263–267, 1983

INTERSTITIAL PULMONARY FIBROSIS IN TWO SISTERS. POSSIBLE AUTOSOMAL RECESSIVE INHERITANCE

Masato TSUKAHARA and Tadashi KAJII

Department of Pediatrics, Yamaguchi University School of Medicine, Ube, Yamaguchi 755, Japan

Summary A 4-year-old girl and her 2-year-old sister both had interstitial pulmonary fibrosis. The parents, unrelated, were free from pulmonary fibrosis as judged from their chest radiographs and pulmonary function tests. The occurrence of the disease in daughters of apparently healthy parents suggests autosomal recessive inheritance, although dominant inheritance with a parent yet to develop the disease can not be totally ruled out.

INTRODUCTION

Interstitial pulmonary fibrosis, also called Hamman-Rich syndrome, is a disease with progressive, diffuse interstitial fibrosis of the lung, leading to dyspnea, cyanosis and congestive heart failure. When familial, the disease is usually inherited as an autosomal dominant gene with low penetrance (McKusick, 1978).

We describe here two sisters with the disease born to apparently healthy parents, a finding suggestive of autosomal recessive inheritance.

CASE REPORTS

Patient 1, a 4-year-old girl, was born after a pregnancy of 40 weeks to a 27-year-old, gravida II, para I mother and a 35-year-old father, both healthy and unrelated. *Patient 2*, a 2-year-old sister of Patient 1, was born after a pregnancy of 40 weeks. Both the patients suffered from progressive dyspnea and cyanosis, but the disease was more severe in Patient 2 than in her elder sister. A 5-year-old elder brother is healthy. Clinical and laboratory findings of the patients are summarized in Table 1, and their chest roentgenograms are presented in Fig. 1.

Biopsy examination of the lung in Patient 2 at 1 year of age revealed extensive increase of connective tissue in the alveolar septa. The alveolar architecture in

Received April 22, 1983

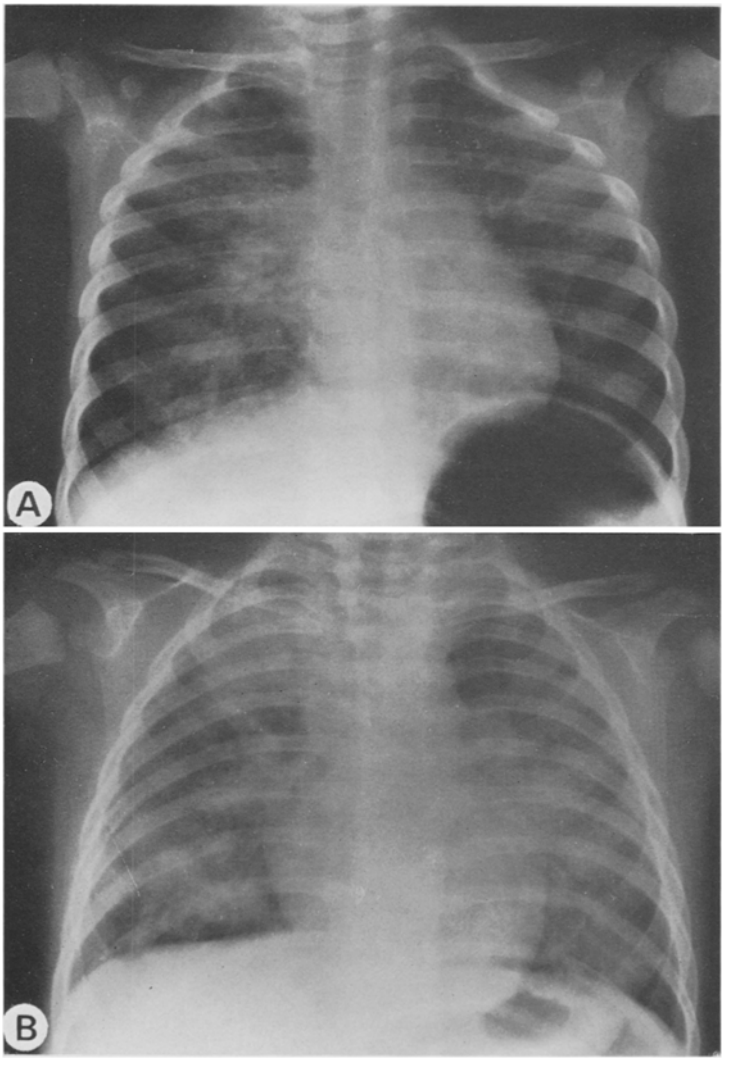

Fig. 1. A: Chest roentgenogram of Patient 1 at 1 year of age. B: Patient 2 at 6 months of age. Diffuse reticular and nodular infiltrates throughout both lungs.

many areas was obliterated or distorted. Most alveoli were lined by cuboidal and hyperplastic epithelial cells.

Family study. Exhaustive questioning of several members of the family revealed no other cases of pulmonary fibrosis (Fig. 2). The maternal grandfather, now 58 years old, suffered from pulmonary tuberculosis at 28 years of age, and the mother also suffered from pulmonary tuberculosis in her infancy. Chest radiographs of the maternal grandmother, parents, and the elder brother revealed no

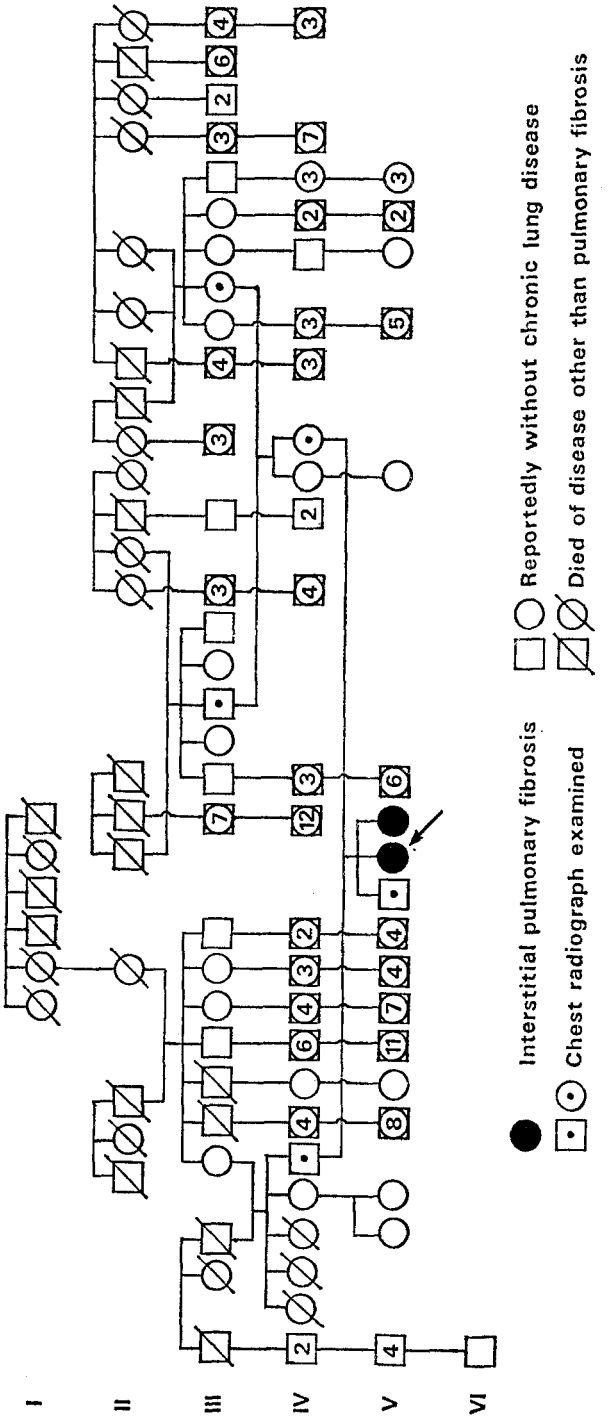

Fig. 2. Family tree. No other cases of interstitial pulmonary fibrosis except Patients 1 and 2.

Table 1. Clinical and laboratory findings of the patients.

	Patient 1	Patient 2
Age (yr)	4	2
Sex	F	F
Growth retardation	−	+
Age at onset (mo)	12	6
Clinical findings		
Cyanosis of the lips and nail beds	+	+
Clubbed fingers	+	+
Precordial buldging	−	+
Cor pulmonale	−	+
Chest radiographs		
Diffuse reticular and nodular infiltrates	+	+
Laboratory findings		
PaO_2 (mm Hg)	49	59.1[a]
$PaCO_2$ (mm Hg)	40	60.5[a]
Treatment	—	+[b]

[a] 50% oxygen was being inhaled at the time of sampling. [b] Prednisolone, digitalis, diuretics and oxygen.

signs of pulmonary fibrosis. A chest radiograph of the maternal grandfather showed calcifications in both upper pulmonary areas and pleuritis in the right base. The paternal grandmother could not attend, but was reportedly well. The paternal grandfather, killed at 53 years of age during the Second World War, was also reportedly well. Pulmonary function tests of the parents were normal including the peak expiratory flow rate, vital capacity, forced expiratory volume, arterial oxygen and carbon dioxide tensions.

DISCUSSION

Familial interstitial pulmonary fibrosis is usually inherited in an autosomal dominant fashion with varying degrees of penetrance and varying timing of onset (McKusick, 1978). The occurrence of the disease in two sisters born to apparently healthy parents suggests autosomal recessive inheritance. A few families have been described in the literature in which the mode of inheritance of the disease was compatible with the autosomal recessive pattern. Donohue *et al.* (1959) described a 3-day-old female infant with congenital interstitial pulmonary fibrosis born to parents who were first cousins. Chest radiographs of the parents were not studied. Davies and Potts (1964) described two brothers, aged 50 and 42 years, both with pulmonary fibrosis. Their parents, apparently healthy, were not studied. Stem-

mermann (1966) reported a Japanese family in Hawaii in which a 38-year-old sister and a 17-year-old brother both had interstitial pulmonary fibrosis. Chest radiographs of their parents, siblings and children revealed no evidence of lung disease.

One of the parents in this case, still young at 29 and 37 years of age, may yet develop this disease. If this would happen, the disease in this case would be compatible with dominant inheritance. Multifactorial inheritance, likewise, can not be ruled out.

Acknowledgement We are indebted to Dr. Y. Yamashita for providing histological findings on lung biopsy specimen from Patient 2.

REFERENCES

Davies, G.M., and Potts, M.W. 1964. Chronic diffuse interstitial pulmonary fibrosis in brothers. *Guy's Hosp. Rep.* **113**: 36–44.

Donohue, W.L., Laski, B., Uchida, I., and Munn, J.D. 1959. Familial fibrocystic pulmonary dysplasia and its relation to the Hamman-Rich syndrome. *Pediatrics* **24**: 786–813.

McKusick, V.A. 1978. *Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive. and X-Linked Phenotypes*, 5th ed., The Johns Hopkins Univ. Press, Baltimore, pp. 336–337.

Stemmermann, G.N. 1966. Chronic familial lung disease. *Am. Rev. Resp. Dis.* **95**: 663–669.