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Familial pulmonary fibrosis: a world without frontiers

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There has been an incredible progress in our understanding of fibrotic lung disorders in the past 20 years. That has led to the development of well-accepted diagnostic criteria for idiopathic pulmonary fibrosis (IPF),[1,2] as well as to the development of two drugs, pirfenidone and nintedanib,[3,4] which are able to slow the progression of the disease and may improve survival. This has been shown in different clinical registries from Australia,[5] Europe,[6,7] and the United States,[8] with an acceptable tolerance profile. In the same period, rare gene mutations associated with familial pulmonary fibrosis (FPF), involving surfactant-related genes (*SFTPA1, SFTPA2, SFTPC, ABCA3*, etc.) and telomere-related genes (TRGs), such as *TERT, TERC, RTEL1, PARN, NAF1, DKC1,* and *TINF2*, have been identified. It has also been shown that the presence of a common gene polymorphism involving the *MUC5B* promoter is a major risk factor for FPF and sporadic IPF.[9] Those seminal studies, along with genome-wide association studies, allowed the genetic basis of IPF to be established.[10,11] More recent studies showed that this genetic basis was shared by non-idiopathic fibrotic lung disorders, such as chronic hypersensitivity pneumonitis,[12] interstitial pneumonia with autoimmune features,[13] and rheumatoid arthritis-associated interstitial lung disease (ILD).[14,15] In the present issue of the JBP, two groups of authors report their experience in the use of antifibrotic agents in IPF and in the characterization of FPF in Brazil.[16,17]

Although there is no consensus definition, FPF is usually defined by a family history of two or more relatives with ILD.[18] The prevalence of IPF is estimated to be 20 per 100,000 population,[19] and approximately 10% of the cases are FPF.[20] Adults with FPF are essentially indistinguishable from patients with sporadic IPF in terms of clinical presentation, radiographic findings, and histopathology, except that those with FPF tend to present it at earlier ages.[21]

In the current issue of the JBP, Hortense et al.[17] report their findings in a sample of 35 patients with FPF. All of the patients were diagnosed with fibrosing ILD and had at least one member in the family with fibrosing ILD. The patients were evaluated between 2014 and 2017. There was no gender predominance, and the median age was quite high (66 years). Smoking and environmental exposure were quite common, being reported in 45% and 80% of the cases, respectively. Among the patients, HRCT patterns were heterogeneous: typical usual interstitial pneumonia (UIP), in 6 (17%); nonspecific interstitial pneumonia, in 9 (26%); organizing pneumonia, in 3 (9%); and chronic hypersensitivity pneumonitis, in 2 (6%). When available, lung histology (n = 6) confirmed the heterogeneity of the HRCT findings. Notably, only 4 patients (11%) had hematological and/or liver disease suggestive of a TRG mutation.[17]

The study by Hortense et al.[17] confirms that patients with FPF can present with a wide variety of clinical features. For instance, a study involving 111 families with FPF compared 309 individuals with ILD with 360 unaffected relatives, revealing that the risk factors for developing ILD were male gender (55.7% vs. 37.2%; $p < 0.0001$), older age (68.3 vs. 53.1 years; $p < 0.0001$), and a history of smoking (67.3% vs. 34.1%; $p < 0.0001$).[21] In addition, a UIP pattern was highly prevalent, being identified in 85% of the patients. However, pathological heterogeneity was observed within individual families—two or more pathological patterns were identified within the affected individuals in 45% of those families, and there was evidence of UIP and nonspecific interstitial pneumonia histopathology in numerous families, suggesting that distinct ILD patterns involve similar pathogenetic pathways.[21] The identification of smoking and environmental exposure as risk factors for IPF illustrates the fundamental interaction between genetic susceptibility and environmental exposure in the development of lung fibrosis,[21] which might contribute to the heterogeneity of the pathological pattern.

An autosomal dominant mode of inheritance with incomplete penetrance is usually observed in FPF.[21] Mutations in TRGs are detected in approximately 30% of the families investigated. A younger age at diagnosis and the presence of hematologic or liver disease are associated with an increased prevalence of TRG mutations in FPF.[10] Such mutations are associated with a worse prognosis and a higher incidence of hematologic complications after lung transplantation in IPF.[22] Less frequently, there can be mutations in surfactant-related genes. In that case, ILD might improve with the use of steroids or azithromycin in children, although there is a lack of evidence of that in adults.[23] However, in most cases (60-70%), FPF remains genetically unexplained and might be related to unique, yet-to-be identified gene mutations or to non-Mendelian genetics associated with environmental risk factors. Hortense et al.[17] suggested that it is necessary to make a precise specific diagnosis for each patient, including pulmonary phenotyping together with the genetic diagnosis, in order to propose and evaluate the treatment. However, access to genetic analysis and genetic expertise is limited, which could be a limiting factor for patients suspected of having a genetic form of pulmonary fibrosis. Novel online

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communication tools might offer an answer to this difficult question. In France, we set up a web-based genetic multidisciplinary discussion (MDD) dedicated to all suspected or confirmed cases of inherited lung fibrosis, using the OrphaLung network of rare pulmonary diseases. That genetic MDD provides an opportunity to discuss cases of suspected genetic forms of lung fibrosis with experts in the interpretation of genetic data, in the monitoring of patients and their family, and in the treatment of those patients. Our genetic MDD is open to international participants. To date, 37 different ILD centers, in nine different countries, have participated and more than 150 cases have been discussed.

There is limited evidence concerning the effects of nintedanib and pirfenidone in FPF. A multicenter retrospective study conducted in Europe and including 33 patients with lung fibrosis and a *TERT* or *TERC* mutation was unable to show any effect of pirfenidone on lung function decline.[24] A post-hoc analysis of two trials identified 102 patients who were carriers of rare variants within one TRG.[25] Those patients had a more rapid decline in FVC than did the patients without a rare variant (1.66% vs. 0.83% per month), and pirfenidone reduced the decline of FVC in that subgroup of patients.[25] National and international guidelines recommend no specific treatment strategy in patients with FPF.[26-28] At our center, we discuss the use of antifibrotic treatment with nintedanib or pirfenidone for every patient with FPF. Various molecules, especially androgens, have the capacity to stimulate telomerase activity.[29] Danazol, a synthetic androgen, has been shown to increase blood leukocyte telomere length in patients with TRG mutations and hematological disorders.[29] Danazol is being tested prospectively in patients with TRG and lung fibrosis (NCT03710356). New molecules targeting the telomere homeostasis system are being developed in an attempt to focus on that specific subgroup of patients.[30]

International collaborative studies are absolutely needed to make further progress in the understanding of lung fibrosis, particularly FPF, an area for which there is a limited number of research centers. It is our shared responsibility to build, maintain, and develop worldwide networks of clinicians and scientists, using all of the modern tools of communication to share data and knowledge, in order to develop new research programs and offer the expertise that patients and their families need and deserve.

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