

Idiopathic Pulmonary Fibrosis-Unknown Cause, Global Occurrence and New Medical Possibilities

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Abstract

During the last few years, idiopathic pulmonary fibrosis seems to have become a serious problem in the area of individual as well as public health. This is why it is necessary to coordinate information about its occurrence, potential risk factors, prognosis, morality as well as new alternatives of treatment. The goal of this article is to provide a brief outline about incidents, etiopathogenesis, clinical signs, prognosis and new drugs. Because of the seriousness and incurability of this disease, it is essential to emphasize a multidisciplinary approach as well as the importance of non-pharmacological interventions for improving life quality.

Keywords: Idiopathic pulmonary fibrosis; Idiopathic interstitial pneumonia; Potential risk factors; Shortness of breath; Lung transplant

Introduction

Diffuse interstitial pulmonary fibrosis (Hamman-Rich syndrome, cryptogenic fibrosing alveolitis) is usually a fatal progressive fibrosing inflammatory lung disease of unknown etiology. This is a disease with characteristic clinic X-ray functional and morphological symptoms [1] American health care uses the term idiopathic pulmonary fibrosis but even this term means, that the etiology is unknown [2]. According to the newest definition, idiopathic pulmonary fibrosis IPF is progressive, fibrosing, interstitial pneumonia of unknown etiology occurring in adult individuals, limited within the lungs and associated with histopathologic and/or radiologic image of common interstitial pneumonia [3]. It occurs similarly to other diseases of the airways or heart and the diagnosis can be complicated. One of the most common symptoms is the unexplainable chronic breathlessness, especially during exercise.

Occurrence

The diagnosis of idiopathic pulmonary fibrosis in patients admitted to an internal medicine clinic is determined in 1-2% of cases, in pathological material about 5% [1]. Incidence of idiopathic fibrosis in Europe and in North America is estimated to be about 3-9 cases per 100,000 residents is gradually increasing.

3 million patients worldwide suffer from idiopathic pulmonary fibrosis. According to the Empire register, there are 149 confirmed patients in Slovakia. The clinical register was established in 2014 and is the database of patients with IPF diagnosis in Central and Western Europe. Statistics show that patients with IPF in Slovakia live over on average 4.98 years. The average age of patients at the time of diagnosis

is 57.2 years and the average age of patients at time of death is 62.82 years [4].

Because the change in terminology and diagnostic criteria in 2002, it is difficult to compare data from the previous period. The same stands for prevention data, which is estimated to be about 14.42% in the United States of America (USA) [3].

Materials and Methods

Etiopathogenesis

Although according to the definition etiology of ILF is unknown, some potential risk factors have been observed such as smoking, work factors, environmental factors (such as metal dust, wood dust, and inhalable chemicals), gastric reflux and micro-organisms, above all viruses which lead to repetitive damage of alveolar epithelial cells [5]. Other factors contributing to the development of IPF are: farm environment-contamination while farming or bird keeping, dust from vegetables and livestock, hairdressing activity, stonemasonry or stone polishing work and diabetes [6].

Family occurrence suggests it is a genetically conditioned predisposition. In sensitive individuals with multiple genetic abnormalities there is an assumption of abnormal lung reparation forming. Family occurrence in 2 or more direct relatives (familial fibrosis) occurs in about 5% of all cases and the disease will develop at an early age [3].

ILF is a complex genetic disease with 11 identified areas that contributes to the development of the disease. Single nucleotide polymorphism (SNP) of the MUC5B gene (rs35705950) is strongly associated with the familial and sporadic form of ILF. Familial IPF is associated with mutations of multiple genes that influence the length of the telomeres (TERT, TERC, DKC1, TIN2, and PARN) [3,5]. In some gene mutations, influence on the disease prognosis is known

(mutations of genes MUC5B, TOLLIP) as well as response to treatment (TOLLIP - carriers of genotype TT, in comparison to genotype CC, profited from treatment by N-acetylcysteine) [5]. Further prospective studies are needed to conclude the clinical use of genetic testing in IPF diagnostics and therapy decision making.

In early stages of the disease, an unknown agent triggers alveolar damage, increases the “permeability” of type I pneumocytes and adjacent capillary endothelium, alveolar and interstitial edema is formed, and the formation of intra-alveolar hyaline membranes occurs. With time, the alveo-capillary permeability and desquamation of intra-alveolar cells increases, intramural inflammation and interstitial fibrosis is formed. Inflammatory exudate is organized in alveolar spaces, fibroblasts proliferation occurs, and the production of fibronectin and collagen increases. Scarring results in the formation of multiple cystic spaces [2].

Pathological anatomy

Macroscopically, the lungs are reduced in size, and they are hard with a grainy surface to touch. Multiple irregular cavities with fibrosis of the surrounding tissue are visible on the cutting surface (so-called honeycombing lungs). In early stages of the disease, we can microscopically observe interstitial fluid and exudate filling the alveolar spaces. Progressively, inflammatory infiltration of intra-alveolar septum occurs, as well as desquamation of alveolar epithelium and hyaline membrane production.

Classification of idiopathic pulmonary fibrosis

According to the consensus ERS/ATS from 2013 [6] the diffusional parenchymal lung diseases (DPLD) are divided into: (Table 1)

Factors of increased mortality with IPF	
Initial factors	Longitudinal factors
Dyspnoe degree	Worsening of dyspnoe degree
DLCO less than 40% RH	Worsening of FVC equal to or more than 10% of absolute value
Desaturation equal to or less than 88% with 6 MWT	Worsening of DLCO equal to or more than 15% absolute value
Range of honeycombing on HRCT Lung hypertension	Worsening of fibrosis on HRCT

Table 1: Factors signalling higher mortality in patients with IPF [3]. (DLCO - diffusional capacity of lung, 6MWT- 6 minute walking test, FVC - forced vital capacity).

- DPLD - with known cause, for example caused by medication or due to systemic connective tissue disease, pneumoconiosis and more.
- Idiopathic interstitial pneumonia
- Granulomatous DPLD - for example-sarcoidosis, Exogenous Allergic Alveolitis (EAA)
- Other forms of DPLD - for example-lymphangioleiomyomatosis

ILF belongs to the idiopathic interstitial pneumonia group (IIP), which is characteristic for isolated lung damage of unknown etiology with various pathologic and radiologic images. IIP is divided into:

Unclassified IIP

Major IIP

- Idiopathic Pulmonary Fibrosis (IPF)
- Idiopathic nonspecific IL
- Respiratory Bronchiolitis-Interstitial Lung Disease (RBILD)
- Desquamative IP (DIP)
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare IIP

- Idiopathic lymphocytic IP (LIP)
- Idiopathic Pleuro Parenchymal Fibroelastosis (PPFE)

Result and Discussion

Clinical picture

The first clinical symptom is mainly dyspnea occurring after exercise (I.-II. degree). A characteristic of IPF is gradually worsening of shortness of breath during the period of several months, often associated with a dry cough. Physical examination typically uncovers an auscultation finding of “dry” crepitation at the bases of the lungs, which resembles the sound of scrunching cellophane or undoing Velcro. A patient often has widened and rounded fingertips that resemble the shape of a wristwatch glass [7]. The patient is usually middle-aged (but can also be significantly young or significantly old). About a third of the patients have repetitive virus infections, shortness of breath is worsening and over time occurs even at rest. The patient is exhausted by cough, weakens, loses weight and gets atrialgia.

In later stages there is cyanosis with respirational insufficiency, rapid shallow breathing during reduction of lung volume with the reduction of lung compliance. When pulmonary hypertension develops, signs of right-sided heart de-compensation may appear.

Diagnostics of idiopathic pulmonary fibrosis

The diagnosis of IPF requires [3,8]:

- The exclusion of other known cause of diffusional lung disorder (e.g. work or domestic environmental exposition, diffusional tissue disorders, drug toxicity).
- Clinical context of IPF and presence of UIP or estimated image of UIP on CT with high resolution computed tomography (HRCT) in patients who did not undergo surgical lung biopsy.
- If the clinical context is atypical for IPF and/or the HRCT image is not defined or a likely UIP image, biopsy of lungs and multidisciplinary consensus is needed to determine the correct diagnosis.
- If biopsic lung sample is not available, it is possible to determine “work diagnosis IPF” on the basis of attentive multidisciplinary evaluation.
- In all patients with IPF, especially with “work diagnosis IPF” the diagnosis of IPF diagnosis should be reevaluated in regular intervals.

X ray image of the chest usually uncovers reticular and reticulomodular dissemination of lower and central lobes. But 10-14% of patients have no abnormalities on the spirometric curve. In later

stages findings may show advanced fibrotic changes (honeycombing) double sided, basal and peripheral, although the finding is often inconspicuous and negative in early stages of the disease. In early stages we can observe a foggy image of “ground glass” (diffused micronodiular shades), which anatomically correlates with alveolitis.

Later, this image is supplemented by thicker reticular and nodular opacities. With progression of the disease, the volume of the thoracic cage decreases (retraction is visible in front-rear projection and side projection). The chest has a lowered activity, the diaphragm is elevated and densifies, widens by mediastinum. The rims of the heart have blurred contours, lung hila are apical. Gradually, small thin-walled cavities of size upto 5-10mm appear, located side by side between reticular opacities.

It is the image of so-called honeycombing lungs in an advanced stage of pulmonary fibrosis [2].

Typical findings from functional lung tests are restrictive ventilatory defect and the reduction of diffusional capacity of the lungs. The diffusional capacity of lungs for CO₂ is lowered practically during all stages of the disease. In advanced stages it occurs between 30-40% of reference value. With the progression of the disease hypoxemia is present even at rest, tension of CO₂ is at standard, hypercapnia develops only in terminal stages. Changes in lung circulation also only reflect fully developed forms of kryptogenic fibrous alveolitis. Firstly, lung hypertension occurs only after exercise, later also occurs at rest with signs of decompensated cor pulmonale [2].

The key examination is high resolution computer tomography (HRCT), which can be sufficient in determining the definite diagnosis of IPF, if typical and likely image of UIP corresponds to the clinical context. In case of indeterminate findings, in order to determine the diagnosis, surgical biopsy of multiple places in lungs and histopathologic examination is needed [3,8].

CT findings more consistent with non-IPF diagnosis still don't eliminate the possibility of IPF if the histopathologic findings are consistent with UIP [8].

During the process of determining the diagnosis, multidisciplinary discussion is usually essential, at least between a pneumonologist and radiologist and in case of histologisation also with a pathologist, who all have experience with IPF diagnostics.

Cellular analysis of broncho alveolar lavage (BAL) is not essential for determining the diagnosis itself, but is fully justified as a part of wider differential diagnostics of diffusional parenchymal pulmonary diseases for the affirmation or exclusion of another alternative diagnosis [1,6]. For example, lymphocytosis in BAL signalizes the possibility of chronic hypersensitive pneumonia in radiologic image of UIP as well [9].

In order to attain an adequate sample of lung for bioptic examination, surgical biopsy of lungs through thoracotomy is needed, or more presently used video-assisted thoracoscopy (VATS) (3). For the successful diagnosis it is inevitable to remove multiple lung tissue samples from various parts of the lungs [3].

Laboratory examination

The sedimentation of erythrocytes is usually increased, as well as immuno complex titres and serum immunoglobulins and cryoglobulines.

In each patient with suspicion of the presence of IPF should have basic examinations done at the time of diagnosis: differential blood count, C-reactive protein, serum creatinin, transaminase, GMT, ALP and serologic diagnostic of the presence of systematic diseases (examination of reumatoid factor, antinuclear antibodies (ANA) and anti-cyclic citrullinated peptide exam (anti-CCP) [3].

In case that during the following progress of the disease signs of possible systemic disease occur, it is needed for these examinations to be repeated, as the lung disability can some-times forego systemic signs.

Systemic diseases may cause pulmonary changes in the UIP image, so it is a condition that they are excluded in the diagnosis of IPF, which, according to the definition, is limited to the lungs [3].

The assumption of IPF diagnosis even with a confirmed UIP image is the exclusion of known-cause lung damage (drug damage, systemic disease, advanced stage of exogenic allergic alveolitis).

Non specified interstitial pneumonia (NSIP) has a similar image, mostly in early stages of UIP, when the “honeycombing” image is not fully developed. Its range is the most important definitive criteria for UIP. It is typical for NSIP to have spared sub pleural areas, which are not typical for UIP. The histologic image with NSIP has characteristic uniform thickening of alveolar walls as a result of fibrosis and inflammatory changes without signs of honeycombing. Fibroblastic knots “foci” are usually not present, or only very inconspicuous.

Treatment of idiopathic pulmonary fibrosis

The traditional treatment by cortico steroids and immune suppressive, which can be very effective with other types of idiopathic interstitial pneumonia which does not give patients with IPF significant benefits, but instead it may cause significant side effects. The PANTHER study [10] showed that in comparison to placebo there was a higher risk of hospitalizations and mortality with the IPF treatment by triple-combination of corticosteroids, azathioprine and N-acetylsteine. The next follow-up of the survey with patient monotherapy by N-acetylsteine was in comparison to placebo also non-beneficial. Studies using other potentially effective drugs such as interferon gamma, bosentan, sildenafil, colchicine, cyclosporin A, etanercept, anti-colagulation, imatinib and other did not show clinically significant/meaningful/influential success [3,11].

Currently, there are two antithrombic drugs approved for IPF treatment, in which it was proved to slow down the progression of the IPF disease: pirfenidone and nintedanib. New studies has shown, that patients with a worse lung function with moderate lung disease still had benefit from the treatment using these drugs.

The present trend is that each patient with IPF should be treated with the mentioned anti-fibrotics. The drugs are approximately equally effective. Present medicine cannot fully treat IPF, which is why the goal of this treatment is mostly to slow down the progression of the disease, avoid additional scarring of tissue and lengthen the patients' lifespan. The secondary goal is to sustain life quality and the highest possible level of activity. The last alternative/option for treatment is a transplant. Patients also undergo additional oxygen treatment.

Pirfenidone is a peroral antifibrotic substance, which inhibits the TGF- β -mediator, which controls multiple cell functions including proliferations and differentiations and has a key role in fibrosis. It also inhibits TNF α cytokinin synthesis with an active role during inflammation [12].

In the ASCEND study, pifendion met the primary goal of the study with a 47,9% reduction of the number of patients who observed worsening of FVC $\geq 10\%$ of reference value or died, as well as a 132,5% increase in the number of patients in which there was no worsening of FVC. Pirfenidone significantly ($p=0,04$) reduced the worsening of exercise tolerance, expressed by the distance traveled during a 6 minute walking test, and lengthened the time of progression of the disease ($p<0.001$) [13]. The analysis id ASCEND and CAPACITY studies showed that in comparison to placebo, the reduction of deaths after a year of treatment by 48% ($p=0.01$) and the risk of death as a result of IPF by 68% ($p=0.006$) [13]. From the spectrum of occurrence of unwanted effects, the majority was gastrointestinal and dermal symptoms (photosensitivity), which only seldom led to the end of treatment.

Nintedanib is a low-molecular inhibitor of tyrosinase including platelet derived growth factor receptors (PDGFR) α and β , fibroblast growth factor receptors (FGFR1-3) and vascular endothelial growth factor receptors. Nintedanib competitively binds to binding sites of adenosine triphosphate (ATP) of these receptors and blocks intercellular signaling. Nintedanib inhibits the activation of signaling cascades FGFR and PDGFR. Which critically join into proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the typical cells in idiopathic pulmonary fibrosis pathology [14].

Studies with nintedanib [14] showed slowing of FVC decrease during nintedanib treat-ment in comparison to placebo by 125.3ml/year ($p<0.001$) in the INPULSIS-1 study and by 93.7 ml/year ($p<0.001$) in the INPULSIS-2 study. Nintedanib also significantly reduced the number of acute exacerbations of IPF. The most common unwanted effects were also gastrointestinal difficulties, vomiting, nausea, and mainly diarrhea, which led to discontinuance of treatment in less than 5% of the patients [14].

Currently, the data about the effect of the treatment in advanced stages of the disease (FVC $<50\%$ RH and/or DLCO $<30-35\%$ RH) is not reliable enough, but post hoc analysis of studies with nintedanib and pifrenidone point out the comparable effect on the slowing of the progression of the disease even in this group of patients [15]. Complex care with palliative interventions ever since the diagnostic is essential for these patients, as well as regular condition check-ups with early indication of long-term home oxygen therapy, comorbidity treatment and mental support by patient organizations as well [15].

It is justified to use systemic corticosteroids with acute exacerbation of IPF and that up to the dose of 1g/day intravenously, even though the benefit of this procedure is not clearly proven [3,11]. Treatment of the gastro esophageal reflux and asymptomatic is suggested, which is a very often finding within patients with IPF (about half of the cases are asymptomatic), and may worsen the progress of the disease.

As from non-pharmacologic interventions lung rehabilitation may be beneficial, in case of hypoxemia and met criteria long term home oxygen therapy (LTHOT) is indicated, and in patients that meet the criteria, also enlistment into the transplant program and lung transplant [3,11]. In case of an "end stage" disease, only maximum palliative care is indicated, artificial lung ventilation for a practically hopeless prognosis is not indicated in most patients with IPF [3,11].

The best way of objective monitoring in the process of the disease is using functional lung tests. It is essential to examine FVC and DLCO, which should be done every 3 months, in individual cases even more often, depending on the condition of the patient during the progress of the disease [3].

The decrease of FVC being $\geq 10\%$ and/or DLCO $\geq 15\%$ indicated progression of the disease. Individual/Each decrease of FVC $<5\%$ and/or DLCO $<10\%$ does not necessarily mean progression, but systemic decrease even of these smaller values is a sign of progression [3].

Regular routine HRCT check-ups are not essential in uncomplicated cases, because the worsening of symptoms and functional parameters reflects the progression of the disease well enough [3].

Echocardiography is indicated for the determination of possibilities of pulmonary hyper-tension especially in case of radically reduced diffusional capacity of lungs (DLCO $<40\%$ RH), which is important from the prognostic view and for early indication of DDOT [3]. Prospectively, we can also expect clinical use of some biomarkers (surfactant protein D, matrix, metalloproteinase 7, CA 19-9, CA-125) [16]. The values of surfactant protein D and CA 19-9 correl with the progression of the disease and marker CA-125 within patients with IPF mortality.

Conclusion

Prognosis

Present-day medicine cannot treat IPF, which is why the goal of treatment is to slow down the process of the disease and avoid additional scarring and lengthen the life of the patient. The secondary goal is to sustain the life quality and highest possible level of activity. The last option of treatment is transplantation. Patients also often undergo additional oxygen treatment.

The prognosis of patients with IPF is in many cases worse than the prognosis of patients with malignant diseases such as carcinoma of prostate, breasts, thyroid and large intestine! The process of the disease can be different:

- Gradually slow, but continual worsening of lung functions and clinical condition
- Fast disease progression
- Transitioned stabilization of the condition
- Acute worsening of the disease

Because of the wide variety of progresses of the disease and range of changes during the time of determining the diagnosis, the evaluation of the patient's condition is complex with the review of the findings at time of diagnose determining (functional test, range and character of changes on HRCT) and evaluation of the dynamics of changes (mostly functional lung tests) during regular monitoring [3]. Factor, that signalizes increased mortality in patients with IPF (Table 1).

In case of an advanced stage disease and fast progression it is needed to consider lung transplantation. From non-pharmacologic interventions in patients with hypoxemia DDOT is indicated in addition to transplantation and lung rehabilitation may be helpful too [17].

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