this advice may be considered as a preventive measure against disease development and complications.

3. After processing the questionnaires, we have grounds to develop further recommendations on nutrition and daily routine that accompany standard treatment regimens to avoid complications of abnormal retinal conditions and worsening of the quality of vision.

4. Analysis of answers in questionnaires is reasonable through determining indices to perform integral evaluation of lifestyle. Rationality index of recommendations through "recommended/not recommended" ratio is the most suitable.

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КЛІНІКО-БІОХІМІЧНА ОЦІНКА СТУПЕНЯ ТЯЖКОСТІ СТАНУ ПАЦІЄНТІВ З ПНЕВМОСКЛЕРОЗОМ РІЗНОЇ ЕТІОЛОГІЇ

Родіонова В.В.
Карасьова О.В.
Шевцова А.І.
Гордієнко Ю.А.
Бех О.Е.
Державний заклад "Дніпропетровська медична академія Міністерства охорони здоров'я України ", м. Дніпро, Україна

CLINICAL AND BIOCHEMICAL ASSESSMENT OF THE SEVERITY OF PNEUMOSCLEROSIS OF DIFFERENT ORIGIN

Rodionova V.
Karasova O.
Shevtsova A.
Gordiienko Iu.
Bekh O.
State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine", Dnipro, Ukraine

Анотація

Під спостереженням знаходились дві групи пацієнтів: 1 – пацієнти з ідіопатичним фіброзом легень та 2 – з системним склерозом, що мали рентгенологічні ознаки пневмосклерозу. Було показано, що візуально-аналогова шкала не є достатньо валідним інструментом для оцінки тяжкості стану пацієнта. Для оцінки

тяжкості стану у пацієнтів обох нозологічних форм рекомендуються шкала задишки mMRC та модифікована шкала Вуда-Даунса. Визначення активності матриксних металопротеїназ 2 і 9 та їхніх комплексів можна розглядати як додатковий прогностичний показник фіброзного процесу в легенях.

Abstract

There were observated two groups of patient: 1 – patients with idiopathic pulmonary fibrosis and 2 – with systemic sclerosis, which had radiological signs of pneumosclerosis. It was shown that the visual analogue scale is not a sufficiently valid tool for assessing the severity of the patient's condition. The mMRC dyspnea scale and the modified Wood-Downs scale are recommended to assess the severity of the condition in patients of both nosological forms. Determination of the activity of matrix metalloproteinases 2 and 9 and their complex forms can be assessed as additional prognostic indicator of the fibrotic process in the lungs.

Ключові слова: пневмосклероз, ідіопатичний легеневий фіброз, системна склеродермія, матриксні металопротеїнази 2 і 9.

Keywords: pneumosclerosis, idiopathic pulmonary fibrosis, systemic sclerosis, matrix metalloproteinases 2 and 9.

Pneumosclerosis is a pathological process in which connective tissue replaces normal lung tissue leading to the development of progressive respiratory insufficiency. Typically, pneumosclerosis develops as a complication of different lung diseases, but when the etiological cause cannot be established, the condition is referred to as idiopathic pulmonary fibrosis (IPF). Depending on the origin of the disease, P. Wolters *et al.* suggest separating pulmonary fibrosis into four groups: 1) driven by epithelial cell dysfunction (*e.g.*, IPF); 2) driven by inflammatory process (systemic sclerosis, rheumatoid arthritis, sarcoidosis, nonspecific interstitial pneumonia, etc.); 3) developed due to occupational exposures or medications (silicosis); 4) smoking-related (desquamative interstitial pneumonia, respiratory bronchiolitis associated with interstitial lung disease, etc.) [1]. Despite various causes of pneumosclerosis, all forms of the disease lead to impaired pulmonary ventilation and bronchial drainage, lymph and blood circulation.

Identification of etiological causes, factors and parameters of pneumosclerosis progression is required not only for correct diagnosis but also for selection of a further strategy of treatment which in the vast majority of cases is aimed at eliminating the underlying pathology and treating chronic pulmonary insufficiency. Prognosis may be relatively favorable when the primary condition is identified and specific treatment methods are used, including immunosuppressive therapy [2]. As for IPF the true etiological cause of the disease is extremely difficult to establish. At the same time, IPF is characterized by a steady progression and high mortality: the average survival of patients with IPF is between 2 and 5 years [3, 4]. In view of the above, early diagnosis of the disease using a procedure which includes analysis of results of clinical examination, laboratory tests, high-resolution computed tomography, surgical or bronchoscopic lung biopsy is highly important [5-7].

It should be noted that IPF diagnosis and prognosis remain a challenge even with all the recommended screening procedures done. Since a surgical procedure performed to obtain pulmonary biopsy specimen is associated with a high risk of complications [8], a crucial task is to find non-invasive markers that can be used as additional tools for diagnosis, assessment of the severity and prognosis of the disease.

One of the promising areas is investigation of matrix metalloproteinases (MMP), which are the calcium-dependent enzymes involved in proteolytic degradation and renewal of connective tissue. The pathobiology of IPF is associated with an excessive synthesis of extracellular matrix (ECM) components and disturbed ECM remodeling mediated by MMPs. Basic research and clinical studies showed an association between the level and activity of some of the 27 currently known MMPs and the development of IPF and its complications [9, 10]. Although the role of gelatinases, or MMP2 and MMP9, is most often discussed in the literature, the diagnostic significance of these enzymes in assessing the severity and prognosis of the disease in patients with pneumosclerosis of different etiologies remains under question.

The aim of the study: to establish clinical and biochemical parameters for assessment of the disease severity and prognosis, based on the results of comparative analysis of clinical data, VAS (Visual Analogue Scale) score and activity of gelatinases in patients with pneumosclerosis of different etiology.

Materials and methods. Thirty-four (34) patients with idiopathic pulmonary fibrosis (IPF), including 24 women and 10 men between 41 and 79 years of age (mean age: 57.56 ± 1.55) participated in this study. IPF diagnosis was based on the clinical and radiographic diagnostic and treatment criteria recommended by ATS/ERS/JRS/ALAT and the Association of Tuberculosis Specialists and Pulmonologists of Ukraine [5, 11].

The second nosological group included 28 patients with systemic sclerosis with radiographic signs of pneumosclerosis. Systemic sclerosis (SS) was diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology, and the 2009 European League against Rheumatism (EULAR) recommendations [12]. Patients with sclerosis included one man and 27 women with radiographic signs of pneumosclerosis, between 19 and 62 years of age (mean age: 39.52±2.11) and the mean duration of the disease of 14.29 ± 1.33 years.

Patients were enrolled in the study if the following inclusion criteria were met: signing of an informed consent form, age between 40 and 80 years, a verified IPF/SS diagnosis with pneumosclerosis. Exclusion criteria included history of any other lung pathology, bronchial asthma, HIV/AIDS, hepatitis B and/or C, tuberculosis of any localization, cancer, and/or surgery performed within 1 year before the study.

All patients underwent examination and treatment in specialized pulmonology and rheumatology in-patient facilities. The examination was performed on admission and after 1 month of monitoring and treatment,

and included documenting complaints and medical history, anthropometric measurements, calculation of body mass index, and measurement of blood oxygen saturation using a pulse oximeter. In addition, to evaluate the severity of dyspnea, mMRC (Modified Medical Research Council) Dyspnea Scale was used. Patients also underwent high-resolution computed tomography (HRCT) and other general clinical tests according to their diagnosis [13, 14]. The standard IPF and SS treatment protocol was in line with international and domestic guidelines [4, 14].

Global severity was assessed using a VAS scale, for which the patient was asked to choose a point on a 10 cm scale reflecting his/her subjective feeling of what difficulties cause him/her clinical manifestations of the pulmonary pathology. The severity was evaluated based on the following symptoms: shortness of breath during exercise, shortness of breath at rest, coughing, sputum production, chest pain, fatigue, weight loss, palpitations. A patient was explained that the starting point (left) corresponded to a good condition, and the end point (right) to a bad condition. The patient had no information on the interpretation of the severity scale.

After self-assessment of severity by the patient, the severity score was interpreted as follows: mild (0-2 cm), moderate (2-5 cm), severe (5-10 cm). The VAS score of >5 cm is considered to have a negative effect on the patient's quality of life.

Clinical data were analyzed using modified Wood-Downes Scoring System (Table 1) [15].

Table 1

Modified Wood-Downes Scoring System

Severity	1	2	3
Respiratory rate	Normal or exceeding the age-appropriate reference value by up to 30%	Exceeds the age- appropriate reference value by 30-50%	Exceeds the age- appropriate reference value by >50%
Oxygen saturation	>95%	90-95 %	<90
Auscultatory findings	Moderate wheezing at the end of exhalation	"Mosaic" breathing pattern, significant wheezing during exhalation	Weakened breathing, significant wheezing during prolonged exhalation, crackles
Use of accessory muscles for respiration	No	Intercostal and subcostal muscles take part in respiration (mild or moderate degree)	Involvement of intercostal, subcostal, suprachoroidal muscles (significant degree), paradoxical breathing
State of consciousness	Not impaired	*Moderately exalted*	Exalted consciousness
PEFR (% of the reference value)	70-90%	50-70%	<50%

Based on the results of severity assessment, patients of each nosological group were sub-divided into two subgroups: Subgroup I included patients with symptoms corresponding to level 1 and 2 of severity according to the Wood-Downes Score; Subgroup II included patients with symptoms of level 3 of severity. The control group consisted of 15 healthy volunteers of matching age.

Additionally, the activities of MMP2/9 and their complexes were evaluated using gelatin zymography. This method includes the following steps: 1) electrophoresis of blood plasma proteins in gel containing gelatin, 2) incubation of gels in buffer containing calcium ions, 3) staining in medium containing Coomassie Brilliant Blue R-250, and evaluation of zones of lysis. This method is used for assessment of the activity of not only mature gelatinases, but also their pro-forms, as well as multienzyme complexes [16].

As a statistical test for group comparison, one-way analysis of variance (ANOVA) was used, followed by the Tukey test. All data are expressed as mean ± standard error of mean (SEM). Results were considered statistically significant at $p<0.05$.

Results and Discussion

Self-assessment of patients with confirmed IPF using VAS scale showed that 21 (61.8%) patients rated their condition as moderately severity and 13 patients (38.2%) as severe. In the group of patients diagnosed with SS, the distribution was as follows: 4 patients rated their condition as mild (14.2%), 20 (71.4%) as moderate and 4 (14.2%) as severe. Comparison of the results of self-assessment with clinical and laboratory data showed an inadequate attitude of patients to their condition, especially in the SS group, which may be related to the long course of illness, gradual development of symptoms and adaptation of patients to their conditions.

Results on the severity of dyspnea assessed using the mMRC Dyspnea Scale are summarized in Table 2, demonstrating more severe condition in patients with IPF.

Table 2

Dyspnea severity in studied patient groups according to mMRC Dyspnea Scale

	Dyspnea grades					Total patients, n (%)
	0	1	2	3	4	
Patients with IPF	0	0 (0%)	5 (14.7%)	17 (50%)	6 (17.7%)	34 (100%)
Patients with SS	0	3 (10.7%)	11 (39.28%)	8 (28.57%)	4 (14.28%)	28 (100%)

Based on the results of evaluation of IPF patients using the modified Wood-Downes Scoring System, the patients were divided into 2 subgroups. Subgroup 1 included 19 patients with mild and moderate disease, with respiratory rate (RR) of 16-19 ± 1 breaths per minute, oxygen saturation (SpO_2) of 85-90%, accessory muscles not involved in respiration, and peak expiratory flow rate (PEFR) of 72-75% of normal value. In subgroup 2 (15 patients) the condition was assessed as severe, with RR of 20-27 ± 1 breaths per minute, oxygen saturation of 45-70%, accessory muscles actively involved in respiration, and PEFR of 72-75% of normal value.

Patients with c SS were also divided into 2 subgroups according to their disease severity based on the modified Wood-Downes score: subgroup 1 included 21 patients with mild and moderate disease, with RR of 16-18 ± 1 breaths per minute, oxygen saturation of 90-94%, accessory muscles not involved in respiration, and PEFR of 72-75% of normal value. Subgroup 2 (7 patients) included patients with severe condition, with RR of 20-24 ± 1 breaths per minute, oxygen saturation of 85-87%, accessory muscles actively involved in respiration, and PEFR of 72-75% of normal value.

Gelatin zymography results showed that patients in study groups developed significant changes in plasma gelatinolytic activity over time (Table 3).

Table 3

Blood plasma gelatinolytic activity (AU) in studied patient groups

Parameter		Control	Idiopathic pulmonary fibrosis		Systemic sclerosis	
			mild and moderate	severe	mild and moderate	severe
proMMP9 (92 kDa)	Day 1	1.05 ± 0.08	1.34 ± 0.21	2.27 ± 0.25**	2.67 ± 0.16****/†††	2.87 ± 0.52**/†
	After 1 month		2.43 ± 0.46**	2.72 ± 0.11***/§§	2.24 ± 0.24	2.91 ± 0.54**/†
MMP9 (83 kDa)	Day 1	1.00 ± 0.09	1.05 ± 0.07	1.56 ± 0.07**/††	1.26 ± 0.07	1.84 ± 0.25**/††
	After 1 month		1.37 ± 0.15	1.66 ± 0.11**/§§	1.68 ± 0.35	1.76 ± 0.25*/§
MMP2 (72 kDa)	Day 1	1.08 ± 0.025	1.12 ± 0.04	1.08 ± 0.01	0.78 ± 0.03****/††††	0.87 ± 0.04
	After 1 month		1.16 ± 0.07	0.93 ± 0.14	0.63 ± 0.30***/§§§§/††††	0.78 ± 0.13*/§§/††
Complex 125-130 kDa	Day 1	0.84 ± 0.08	1.06 ± 0.17	1.55 ± 0.22	-	-
	After 1 month		2.50 ± 1.50*/†	2.14 ± 0.20**	-	-
Complex 120 kDa	Day 1	0.91 ± 0.10	0.62 ± 0.12	0.47 ± 0.10	1.52 ± 0.20*	1.71 ± 0.88
	After 1 month		1.96 ± 0.37*/§§§	0.81 ± 0.10	3.31 ± 1.40**/§/††	3.41 ± 1.66****/§/†††

Note: * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 compared to control group, § p<0.05, §§ p<0.01, §§§ p<0.001, §§§§ p<0.0001 – compared to parameters of the respective group of patients on Day 1, †† p<0.01, †††† p<0.0001 – significance level in patients with mild and moderate idiopathic pulmonary fibrosis on Day 1. AU – arbitrary units.

The data summarized in Table 3 show that the activities of a pro-form and mature MMP9 in all study groups were above normal value and were associated with the disease severity. It should be noted that proMMP9 activity was significantly different in patients with IPF and SS: in the latter group it was significantly higher. In contrast, MMP2 activity did not change in IPF group, while in patients with systemic sclerosis this parameter decreased significantly, and

over time a further decrease in MMP2 activity was observed.

The advantage of the method chosen for assessment of the activity of matrix metalloproteinases is that using this method different forms of MMP with gelatinolytic activity can be studied. For example, at the beginning of testing, in IPF patients, in addition to typical MMP2 and MMP9, blood samples showed zones of lysis of gelatin in the range of 125-130 kDa, as well as a zone with a molecular weight of 120 kDa. Enzymes corresponding to these zones were referred to as the 125-130 kDa complex and the 120 kDa complex, respectively. Our results showed that the activity of these complexes in patients with IPF increased significantly after one month of monitoring. In contrast, in patients with SS the 125-130 kDa complex was absent, while the activity in the zone of 120 kDa significantly exceeded normal value and was 2-3 times higher than that in the IPF group, and in addition was associated with the severity of the disease.

Analysis of publications suggests that the 125-130 kDa form is an MMP9 complex with lipocalin. Lipocalin is expressed in very low concentrations in many human tissues, but is mostly synthesized by neutrophils, therefore, in the literature it is most frequently referred to as neutrophil gelatinase-associated lipocalin (NGAL) [17]. Human neutrophils simultaneously express NGAL and gelatinase B (MMP9, 92 kDa), which are stored in specific granules and secreted upon activation of these cells. In this case, NGAL can be secreted both as a monomer and as a heterodimer, in form of a complex with MMP9 with a molecular weight of 125 kDa. Apparently, the increase in the activity of the 125-130 kDa complex that we observed in the blood of patients with IPF, was associated with the involvement of neutrophils in the development of pneumosclerosis. There are studies supporting this hypothesis that demonstrated that NGAL expression was associated with inflammation and proliferation processes, endothelial dysfunction, and other pathological conditions [18-20]. Further, evidence suggests that formation of MMP9/NGAL complexes help to preserve the activity of this gelatinase and improve lung oxygenation [21]. As to the 120 kDa complex, no evidence was found. Apparently, analysis of composition of this complex could provide additional information about the mechanisms causing its increase in patients with systemic sclerosis and its possible role in the pathogenesis of this disease.

Conclusions

1. To assess the severity of dyspnea in patients with IPF and SS complicated by pneumosclerosis, we recommend using mMRC scale.

2. Visual analogue scale cannot be considered a valid tool for disease severity assessment. For clinical data analysis, the modified Wood-Downes Scoring System is suggested for severity assessment in patients with IPF and SS complicated by pneumosclerosis.

3. Evaluation of the activity of MMP2/9 and their complexes can be used as an additional prognostic parameter of pulmonary fibrosis and reflect the severity of the pathological process.

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PECULIARITIES OF PRIORITIES OF TREATMENT GENERALIZED PARODONTAL DISEASES IN PATIENTS WITH ANOREXIA NERVOSA

Antonenko M.
Head of Department of Dentistry, Institute of Postgraduate Education, Bogomolets National Medical University, Kiev,Ukraine,
Reshetnyk L.
Department of Dentistry, Institute of Postgraduate Education, assistant professor,
Zelinskaya N.
Department of Dentistry, Institute of Postgraduate Education, associate professor

Abstract

Early diagnosis of the initial degree of generalized parodontitis (GP) is an effective way of secondary prevention. The aim of this research was to develop a protocol for the treatment of GP in patients with AN. The object - 60 patients (mean age 26±3.8 years), with a diagnosis of GP, I-II degree, chronic, and AN, restrictive, which by simple randomization were divided into three groups (randomized by sex, age of patients, underlying and comorbidy diagnosis) to study the clinical effectiveness of our proposed method. Clinical, radiological, hygienic, immunological, biochemical, psychological and statistical methods were used. Thus, as a result of the proposed treatment protocol, the largest number of satisfactory treatment results was observed in group III patients (85.0±8.0%) with the inclusion of drugs that affect the pathogenetic mechanisms of the disease, including normalization of local immunity, markers of decline oxidative-antioxidant stress, radiological data of normalization of bone tissue of the alveolar process, a tendency to reduce microbial and tissue sensitization.

Keywords: generalized parodontal diseases, generalized parodontitis, hypersensibilisation, anorexia nervosa, microbial allergy, osteoporosis.

Generalized parodontal diseases (GPD) consistently occupy one of the leading places in the structure of dental diseases. According to epidemiological researches, these diseases affect more than 95% of the world's population over 45 years, and among people aged 31-44 years, the prevalence of pathology is over 75%, which indicates not only high levels of morbidity, but also a significant reduction in the patients'age [1]. In the structure of parodontal diseases, 90% of it are inflammatory and dystrophic-inflammatory processes and the authors note a steady trend towards the predominance of dystrophic-