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Multiple Hormonal Dysregulation as A Determinant of Exacerbation Frequency in Female Chronic Obstructive Pulmonary Disease Patients.

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ABSTRACT

The endocrine glands take active part in human organism adaptation to various physiological and pathological stimuli. Many researchers noted the close relationships between the endocrine system dysfunction and the course and prognosis of chronic obstructive pulmonary disease. Female patients with moderate and severe chronic obstructive pulmonary disease (COPD) stage II and III were included in the study. The signed informed consent form was obtained from each enrolled patient. The spirometry was performed, the concentrations of cortisol and DHEA-S were determined, and the frequency of disease exacerbations. The conducted analysis had reveled the significant differences between cortisol and DHEA-S parameters. Cortisol, the most precise marker of adrenal cortex condition, plays significant role in determining the clinical course of the disease. Also the reverse correlation between the level of hormones and the age and disease duration was found. The severity of cortisol and DHEA-S synthesis disturbances is tightly correlated with the severity of bronchial obstruction (FEV1) and the frequency of exacerbations. The revealed hormonal status changes in COPD patients provide the basis for correction of these parameters in complex treatment of COPD in order to prevent the disease exacerbations.

Keywords: chronic obstructive pulmonary disease, hormonal dysregulation, survival (time-to-event) analysis

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INTRODUCTION

COPD is the fourth most prevalent cause of death worldwide [1] and poses the serious treat for the people's health although preventable and treatable. COPD exacerbations (periodic worsening of cough, dyspnea and sputum production) contribute seriously into pulmonary function impairment, lower the quality of life and increase the need for urgent care and hospitalizations as well as the cost of treatment. The frequency of exacerbation occurrence varies significantly in different patients [2]. The large amount of data was collected with patients' examination using the GOLD spirometric classification [4].It was found that the risk of exacerbation, hospitalization and death increases with the worsening of airflow parameters. The results of studies conducted during last decades had improved the understanding of COPD pathogenesis and had broaden the therapeutic options. COPD patients typically have systemic non-pulmonary symptoms related to the range of hormonal disturbances. It is known that COPD often coincide with adrenal system imbalance. The most important factor in this condition is the decrease in cortisol and DHEA-S concentrations [3,5–10]. There is also a large body of publications on COPD exacerbation prevention. It ought to be understood that every COPD exacerbation worsens the course of the disease, therefore the maximal effort should be taken to prevent the disease exacerbation.

Thus, the aim of the study is the investigation of disease course particularities, the diagnostic and prognostic value of steroid hormones (cortisol, DHEA-S) as well as the analysis of exacerbation occurrence in patients with moderate and severe COPD for 12 month [11].

MATERIALS AND METHODS

Female patients with moderate and severe COPD stage II and III were included in the study. COPD diagnostics, stage and severity determination were conducted according to recommendations of European Respiratory Society (2011), Russian Federal COPD program (2004), the international program "COPD Global Initiative (GOLD)(2010, 2011)", National pulmonology guidelines (2009) and International Classification of Diseases, 10th revision (ICD-10) (WHO, Geneva, 1992) [4, 5, 9].The signed informed consent form was obtained from each enrolled patient. The controlled study of disease clinical manifestations and recording of subjective and objective parameters of internal organs and systems examination was done on Day 1 of hospitalization and on Days 13–14 of treatment. During the study, the clinical symptoms were evaluated using point system. The spirometry was performed with the measurement of FEV_1, IVC, FVC and FEV_1/FVC ratio.

Furthermore, the cortisol and DHEA-S levels were determined by automated ELISA with Emmulite instrument.

During the study, the frequency of disease exacerbations was assessed which was determined based on the clinical manifestations of complaints on acute exacerbation of disease symptoms and on particular instrumental and laboratory findings (CBC, chest X-ray, ECG, blood biochemistry and microbiological analysis of the sputum).

Statistical processing of the data was done using Microsoft Excel spreadsheets, STATISTICA v6.0 software package and SPSS software package. The quantitative data (with normal distribution) is presented as $M \pm SD$, where M = cohort mean and SD = standard deviation. For correlation analysis of evaluated parameters, the Pearson parametric method and Spearman non-parametric method, were used.

The survival (time-to-event) analysis was used for the exacerbation event assessment. This statistical method analyzes the period of time from the pre-determined initial time until the determined outcome event. This method allows the description of any dichotomic outcome which occurs only once during observation (time to COPD exacerbation development).The method has an advantage of using the data of all patients which allows for more precise determination of the mean survival time. The methods for analysis of event occurrence time also include Kaplan-Meier method. For censored but not grouped life span observations the exacerbation function can be assessed directly.

RESULTS

In order to evaluate the influence of hormonal disturbances on the course of COPD, 56 women were examined. It was found that in all patients with moderate COPD the baseline cortisol level was decreased with the average of 71.86 ± 11.87 mmol/L (Fig. 1). In patients with severe COPD, the average cortisol levels was 28.8 ± 08.27 mmol/L.

The correlation analysis revealed the reverse correlation between the cortisol level and age (0.57**) and between the cortisol level and the duration of the disease (0.56**)(** – correlation significance at 0.01 level).During the study, the analysis of hormones had found the significantly lower estradiol levels in 22 % female patients with moderate COPD and in 54 % of women with severe COPD (the average estradiol concentration in fertile women was 22.9 ± 0.3 pg/mL. Particular attention was paid to the assessment of androgenic status of female COPD patients. The total testosterone level in examined females with moderate COPD was 0.25 ± 0.69 ng/mL, which was 2 times lower than that of the control group of healthy women of reproductive age (0.56 ± 0.5 nmol/L, p<0.05) The DHEA-S concentration (0.78 ± 0.15 micromol/L) in female COPD patients was also significantly lower than in healthy women group (1.8 ± 0.9 micromol/L, p<0.05), but remained in normal range (0.57 ± 3.8 nmol/L). However, the DHEA-S level in menopausal women was lowered in 84 % of cases and very low numbers (less that 0.1 microgram/mL) were noted in almost two thirds of patients. During the study, there was no correlation found for the estrogen (estradiol) levels and the age and disease duration of COPD, but the correlation between androgens (testosterone and DHEA-S) with the age and disease duration either in fertile or postmenopausal women, was confirmed (r = 0.52**, r = 0.48**).

For aldosterone levels, the close correlation was found with the disease duration (r = -0.84, p<0.001) and the age of patients (r = -0.59, p<0.001). The deficit of aldosterone was determined in 49 % of patients. The lowest aldosterone concentrations were found in COPD patients with the disease history longer that 20 years and in those using high doses of inhalation glucocorticoids.

For the exacerbation occurrence assessment, we defined 2 groups of patients according the concomitant hormonal disturbances. In the compared groups of patients with moderate COPD without hormonal disturbances the exacerbations were reported by 10 patients (22.7 %). The exacerbations factor was 0.27 per patient per 3 month. After 12 months the exacerbation factor was 0.86 per patient.

The time until the first exacerbation occurrence (mean (range)) was 134 (100–160) days. In the group of patients with moderate COPD with hormonal disturbances the exacerbations were reported by 16 patients (29.09 %), the exacerbation factor was 0.29 per patient per 3 month and 0.9 for 12 month, accordingly.

The time until the first exacerbation occurrence (mean (range)) was 118 (95–140) days. It is worth noting that the most exacerbations occurred during acute respiratory infections. In the group of patients with severe COPD the exacerbation occurrence was as follows: in the group without hormonal disorders – in 20 patients (36.3 %) after 3 months of observation, exacerbation factor 0.36 and 1.03 after 12 month (per patient); in the group with hormonal disorders – in 24 patients after 3 month of observation, exacerbation factor was 0.4 and 1.2 after 12 months of observation (per patient).

DISCUSSION

During the study and by the results of comprehensive examination of 56 female patients with moderate and severe COPD we had found that the decline in adrenal cortical hormones as well as the decline in testosterone and estradiol levels are found significantly more often in COPD patients than in healthy subjects. The majority of examined patients had one or another adrenal cortical hormone insufficiency with the glucocorticoid insufficiency being the most prevalent. Furthermore, it was shown that all clinical parameters defining the course of COPD were dependent upon the levels of all hormones. Moreover, it was determined by the assessment of exacerbation occurrence that the concomitant hormonal disorders correlate with greater number of COPD exacerbation events and with the shorter time until the first exacerbation occurrence.

CONCLUSIONS

COPD is the example of multifactorial disease. The investigation of hormonal status effect of frequency of exacerbation occurrence with help in understanding the effect of certain hormones on inflammation regulation in COPD

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