

ORIGINAL PAPER

Chronic Airflow Obstruction Syndrome Due to Pulmonary Tuberculosis Treated with Directly Observed Therapy – a Serious Changes in Lung Function

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The origin of Chronic airflow obstruction (CAO) syndrome in active Tuberculosis (TB), despite significant similarities with chronic obstructive pulmonary disease (COPD), still remains unknown. **The aim** of the study was to examine the potential causes and risks for the development of CAO syndrome in new cases of pulmonary TB. **Design:** Prospective, nest case-control study. **Patients:** 40 patients with newly detected cavitary pulmonary TB and initial normal respiratory function, diagnosed and treated according to DOTS strategy. **Measurements and results:** The average values of Snider's radiological score during TB treatment were significantly reduced ($p < 0.001$), as well as average values of non-specific systemic serum markers of inflammation. The average values of FEV₁ (%), both before, during and at the end of completion of TB treatment were significantly decreased ($p < 0.05$). Linear regression analysis confirmed a statistically significant association between changes in the values of FEV₁ (%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture conversion rate. From the initial findings of normal pulmonary ventilation tests, upon the completion of TB treatment 35.0% of observed patients developed the CAO syndrome. Logistic regression analysis confirmed a positive familiar burden for COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture, as statistically significant predictors, while multivariate logistic regression analysis confirmed Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture as most significant risk factors for CAO syndrome occurrence and development. **Conclusion:** The CAO syndrome is often a consequence and significant functional impairment of the respiratory system, during the reparative processes in active TB, even in the absence of risk factors for COPD. Only microbiological cure of TB patients with underlying risks for disorders of lung function, is not sufficient and effective approach for prevention of their further potential health deterioration. **KEY WORDS:** TUBERCULOSIS, BRONCHIAL OBSTRUCTION, RISK FACTORS, COPD.

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1. INTRODUCTION

The association of tuberculosis (TB) and airflow obstruction significantly more difficult and prolong the course of the specific process in the lungs, while extensive (cavitary) forms of pulmonary TB, with its long-term evolution in cases of bronchogenic forms of the disease, contribute to severe destruction of lung parenchyma. On the other hand, inadequate treatment of bronchial obstruction in patients with active TB can, ultimately, lead to the chronic airway obstruction (CAO) syndrome, with clinical manifestation very similar to that in chronic obstructive pulmonary disease (COPD), but in spite of certain analogies in the etiopathogenesis, clinical, and functional manifestations of these two entities, they should not be equated, but should be differentiated on time (1).

Causes and development of airflow obstruction in patients with active TB, in addition to the factors of infection, involving other contributing factors to the host (patient), as well as from the environment, while clinically manifested bronchial obstruction occurs as their mutual interplay (2). Identification of these risk factors is the key for better understanding the development of bronchial obstruction in active pulmonary TB, as an important step in further implementation of existing strategies of TB control and treatment. Bearing in mind the global significance of TB and COPD burden, the existing specificity and analogy in pathogenesis of CAO,

with other bronchial obstruction clinical syndromes and diseases, especially COPD, will be more accurate and with a clear distinction to the initially, very often unrecognized, coexisting bronchial obstruction comorbidity in patients with active pulmonary TB (1, 3).

2. AIM OF THE STUDY

The aim of the study was to examine the potential causes and risks for the development of CAO syndrome in new cases of cavitary pulmonary TB, with initial normal respiratory function, treated with directly observed therapy in the standard six-months regimen, according to the hereditary burden of COPD, air pollution in living and working environment, cigarette smoking habits and level of nicotine dependence, radiological extent of specific lesions in lungs, sputum conversion rate and non-specific systemic pro-inflammatory indices.

3. MATERIAL AND METHODS

The research was performed as a prospective, nest case-control study, in the Clinic for lung diseases, Clinical Centre of Nis, on the planned 40 patients with newly detected cavitary pulmonary TB and initial normal respiratory function, diagnosed and treated according to DOTS strategy and National TB Programme of the Republic of Serbia, in the period from January 2005 until the June 2010 year (y).

Inclusion criteria of patients for entering in the research were: a) typical symptoms of pulmonary TB (cough, sputum production, fever, night sweats and weight loss); b) negative personal history of TB and/or TB treatment; c) fibrocavitary pulmonary infiltrates on standard chest radiographs; d) at least one smear positive sputum, with the subsequent positive culture on *M. tuberculosis*; and et all research subjects, at the time of the inclusion in the study, could already been on the antituberculosis treatment, but not more than two weeks. The exclusion criteria were: a) detection of mono, or multi-resistant TB bacilli in the first positive sputum culture; b) coexisting lung disease, defined as post tuberculosis residual fibrosis, and/or clinical, laboratory, radiology and/or histopathological con-

firmation of lung pathology other than TB; c) patients with chronic heart and/or kidney failure and/or chronic metabolic disorders. Risk factors for COPD data, in terms of: familial burden, potential exposure to air pollution in living and working environment for more than 15 years and smoking habits (indexed as pack/year) were determined by taking medical history data, while the nicotine dependence was determined by initially filling the specific questionnaire of Fagerst rm's test for nicotine dependence (4, 5).

All tested patients were made standard chest radiographs in posterior-anterior projection at the beginning of TB treatment and after the six months, at the end of the same. Interpretation of radiological extent of the disease was performed without access to the values of parameters of lung function, and were scored according to the Snider scoring system (6).

All bacteriological sputum analysis were performed according to principles of National TB Programme of the Republic of Serbia (4).

There were determined: erythrocyte sedimentation rate (SE) in the first hour (mm/1h), peripheral blood smear, which was obtained white blood cell count (WBC) ($10^9/l$), serum levels of C-reactive protein (CRP) (mg/l) and fibrinogen (g/l), at the beginning of TB treatment and after the 6 months, upon the completion of same.

Lung function testing was carried out by spirometry, determined the: a) forced vital capacity-FVC; b) forced expiratory volume in first second- FEV_1 and their percentage ratio- $FEV_1/FVC \times 100\%$. All of the patients, before entering the study were performed a pharmacodynamic bronchodilatation test of reversibility, by inhalation of 400 μg salbutamol metered dose inhalation spray with re-measurement of FEV_1 after the 30 minutes of inhalation. Positive test was consider as a increasing the FEV_1 for 200 ml or 12% and more from the baseline level. Criteria for bronchial obstruction were: $FEV_1/FVC \times 100\% \leq 70\%$ and level of post bronchodilatation $FEV_1 \leq 80\%$ of the reference values. Spirometry were performed: a) at the beginning of the initial phase of TB treatment, b) after the

2 months of the same and c) upon the completion of the whole TB treatment (after the 6 months).

Statistical analysis was performed on the PC. For entering, ranking, clustering, tabular and graphical display of data was used Excel program from Microsoft Office 2003 software package. All calculations were performed using SPSS program.

The values of characteristics at the beginning and end of treatment of observed patients were compared by Wilcoxon's Signed Rank test. Comparison of mean values of numerical characteristics between the three measurements of lung function, was done by Single Factor analysis of variance (One way ANOVA), forwarded with Turkey post hoc test. Analysis of the relationship between changes in FEV_1 or FVC values during the treatment of TB and value factors of interest was performed by univariate linear regression analysis (calculated the linear regression coefficient (β) and its 95% confidence interval). The statistical significance of the regression coefficient is checked by t-test. To assess the impact of factors of interest in the development of CAO syndrome there were applied the logistic regression analysis. Approximate values were calculated relative risk (odds ratio-OR) and their 95% confidence interval. Assessing the value of statistical significance was performed by calculating the OR Wald values. Factors for which the univariate logistic regression showed that significantly influence the occurrence of CAO syndrome, were included in multivariate regression models. By applying the method step by step backwards (Backward: Wald), from the multivariate model are excluded those factors whose impact was not statistically significant. As the threshold of statistical significance level was used to estimate errors of less than 5% ($p < 0.05$).

4. RESULTS

The average age of observed patients was 47.1 ± 15.50 y, of which 62.5% were men and 37.5% women. In the social structure, there were dominated employees (35.0%) and students (15.0%), while the minimum were registered among displaced persons and farmers (5.0%). From the city population be-

Serum markers of inflammation	Beginning of TB treatment	End of TB treatment	Comparison of values at the beginning and end of the TB treatment*	The difference between value at the beginning and end of the TB treatment
SE (mm/1h)	58.53±29.60	10.85±9.25	Z=5.39 i p<0.001	47.67±27.88
WBC (109l)	9.14±2.95	6.61±1.07	Z=4.64 i p<0.001	2.52±2.79
CRP (mg/l)	51.90±42.07	4.37±3.72	Z=5.50 i p<0.001	47.52±40.44
Fibrinogen (g/l)	6.80±3.11	2.96±1.02	Z=5.26 i p<0.001	3.84±2.92

TABLE 1. Comparing the values of non-specific systemic markers of inflammation. (Note: * - Wilcoxon Signed Ranks test;)

Lung function parameter	I measurement	II measurement	III measurement	Comparison of values between tests *
FVC (%)	97.10±11.12	99.52±10.75	101.12±11.66	I vs II: p<0.01 II vs III: p<0.05 I vs III: p<0.001
FEV ₁ (%)	92.90±11.00	92.50±13.9	88.53±15.83	II vs III: p<0.05 I vs III: p<0.05
FEV ₁ /FVCx100%	78.02±6.31	76.04±6.99	73.22±8.68	I vs II: p<0.05 II vs III: p<0.05 I vs III: p<0.01

TABLE 2. Comparing the values of lung function parameters between the three measurements made. (Note: * - ANOVA i Tukey post hoc test;)

longed 60.0% of patients and the ratio of urban and rural population did not show statistically significant differences. According to medical history, patients were initially cited, as most frequently respiratory symptoms: cough (97.5%), expectoration (87.5%) and dyspnea (67.5%), and from general symptoms fever (27.5%) and night sweats (67.5%). The average duration of symptoms, till the first appearance of a doctor were 66.40 ± 63.88 days.

Familiar burden for COPD or asthma was registered in 22.5% of patients and continuous exposure to air pollution of more than 15 years, was registered in only 15.0% of patients in their surrounding outdoor living environment, with regard to 20.0% of them in an indoor living space, while in 22.5% patients were registered occupational exposure to different allergens and respiratory irritants in the workplace. Initially, positive physical examination on bronchial obstruction was registered in 35.0% of patients, while the initial bacterial infection of upper respiratory tract were in 22.5%. The majority of patients were current smokers (52.5%), with average pack/year index of 1.24±0.43/25.64±9.25, while 2.5% of them belonged to a group of ex-smokers, with an average time of quitting of 0.91 ± 3.01 years. Only 45.0% of observed patients were non-smokers. There were registered a high level of nicotine dependence of average 6.73 ± 1.93 Fargestörm score points, while

86.4% of the patients had high and very high level of nicotine dependence. Generally, 37.5% patients had no any risk factor for COPD.

Average Snider's radiological score during TB treatment were significantly reduced from 8.02±3.06 score points at the beginning, to 3.13±1.38 at the end of the same, which is significantly lower value (Z=5.53, p<0.001; Wilcoxon Signed Ranks test;), with average score reduction of 4.90 ± 2.12 score points. The average sputum conversion smear rate (microscopy) was 3.13±2.77 weeks, while on culture it was 4.0±2.34 weeks. Average values of non-specific systemic serum markers of inflammation were statistically significantly reduced during the TB treatment (Table 1).

Positive bronchodilation test was verified in 15.0% of patients, but the average values of FVC, both before and during, as well as at the end of the TB treatment, were statistically significantly increase, as opposed to the values of FEV₁, which have decreased after the completion of the same, but with statistical significance too (Table 2).

Linear regression analysis confirmed a statistically significant association between changes in the values of FEV₁(%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture conversion rate. Any increase in Snider's radiological score at the beginning of TB treatment and a slower sputum culture conversion rate during the same, for just one measurement unit, is associated with statistically significantly higher decrease in the FEV₁(%) after the treatment completion, as follows: Snider's radiological score of 0.587% (0.138-1.036%, p <0.01), a sputum conversion rate on culture for 1.598% (0.204-2.992%, p <0.05) (Figure 1).

From the initial findings of normal pulmonary ventilation tests, upon the completion of TB treatment 35.0% of observed patients developed the CAO

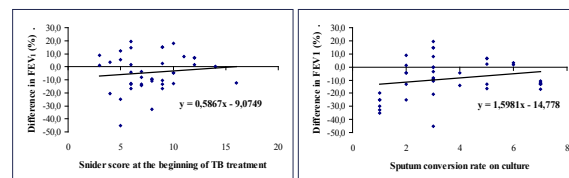


FIGURE 1. The association between Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture with changes in the value of FEV₁(%) occurred during TB treatment

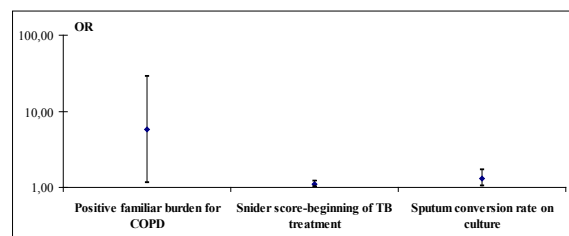


FIGURE 2. Predictors for the occurrence and development of CAO syndrome.

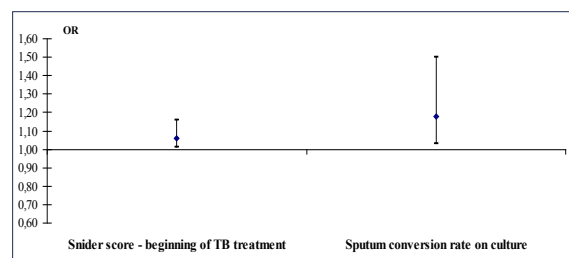


FIGURE 3. OR values and their 95% CI to assess the impact of Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture as a major risk factors for the development of CAO syndrome.

syndrome. Logistic regression analysis was observed in the group of potential risk factors for COPD, factors of TB activity and factors of systemic inflamma-

tion, as well as statistically significant predictors for the occurrence and development of CAO syndrome in observed patients, after the completion of TB treatment, confirmed a positive familiar burden for COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture. In patients who have had a positive familiar burden for COPD, the risk for the onset and development of CAO syndrome after finishing the treatment of TB was significantly higher 5.75 times (1.16 times to 28.55, $p < 0.05$), while any increase in value of Snider's radiological score at the beginning of TB treatment to 7% (2-21%, $p < 0.04$) and the sputum culture conversion rate of 21% (6-69%, $p < 0.05$), was also statistically significantly increased the risk for developing the CAO syndrome in these patients (Figure 2).

Multivariate logistic regression analysis, as statistically the most significant predictors for the development of CAO syndrome in the observed patients allocated Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture, so that each of these factors increase the value for the one measurement unit, therefore is significantly increased risk for developing CAO syndrome: Snider's radiological score at the beginning of the TB treatment for 6% (1-16%, $p < 0.05$), and sputum conversion rate on culture for 18% (30-50%, $p < 0.05$) (Figure 3).

5. DISCUSSION

Although the extensive destruction of lung parenchyma in TB, with consequent restriction of airflow through the bronchial tree is clinically relatively common, the severity of bronchial obstruction and bronchodilator response, have not been evaluated objectively till these days. The severity of bronchial obstruction increases with numbers of smoked cigarettes, initial radiological extent of pulmonary TB lesions, as well as clinical course and duration of active non-recognized and non-treated disease (6). These patients in everyday clinical practice, most all of their symptoms and limitations, due to residual bronchial obstruction, consider as a consequence of cured TB and in most cases ignoring the emergence of

severe clinical manifestations and complications (7).

Reviewing the smoking habits of patients in our study, current smokers accounted for more than one half (52.5%), while former smokers were 2.5% and the number of non-smokers has moved to more than one third of patients (45.0%), which is corresponding to the data in studies of Kollapan and Gopi (8). The average pack/years index in current smokers was 1.24/25.64, with a high level of nicotine dependence, of 6.73 Fagerst rm's score points, which corresponds to the results in several large population surveys across the European Union, among the population in areas with high TB incidence and significant air pollution (9, 10, 11). In our investigation, continuous exposure to air pollution in period for more than 15 years, was registered in only 15.0% of patients in their surrounding outdoor living environment, with regard to 20.0% of them in an indoor living space, while in 22.5% patients were registered occupational exposure to different allergens and respiratory irritants in the workplace. In general, without the examined risk factors for COPD, there were registered just 37.5% patients, which corresponds to the results of similar studies in literature (3, 6, 7).

Although all the mechanisms of systemic inflammation in the pathogenesis of bronchial obstruction in TB patients remained still unclear, it is certain that it acts in active TB as an exclusively linked. Our research registered initially pathologically elevated the mean values of serum markers of acute systemic inflammation, which by the end of treatment significantly decreased to normal ones, or subclinical, which can explain by the high intensity of infection in active extensive TB, as well as their decline by the end of TB treatment, due to antituberculotics (6).

Positive bronchodilatation test was verified in only 15.0% of observed patients, which doesn't correlates with the available data in the literature, considering the fact that in patients with active pulmonary TB, this test is positive in overall 44% -88% (3). Anyway, the average values of FVC, both before and during, as well as at the end of the TB treatment, were statistically signif-

icantly increase, as opposed to the values of FEV_1 , which have decreased after the completion of the same, but with statistical significance too, which confirms the possible of reparative processes during the TB healing as a significant factor for the developing CAO syndrome lately (12, 13, 14).

In our study, by the linear regression analysis we confirmed a statistically significant association between changes in the values of FEV_1 (%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture conversion rate, while logistic regression analysis confirmed a positive family history of COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture, as statistically significant predictors for the occurrence and development of CAO syndrome in observed patients, after the completion of TB treatment. Multivariate logistic regression analysis, as statistically the most significant risk factors for the development of CAO syndrome in the observed patients allocated in our investigation Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture.

According to the results in our investigation, the influence of positive familiar history on COPD, initial radiological extent of specific pulmonary TB lesions, as well as sputum conversion rate on culture, in patients with active pulmonary TB for the CAO syndrome onset, are significant as a predictive factors for residual bronchial obstruction upon completion of TB treatment (13). Strong correlation between the initial extent of radiological pulmonary specific lesions and sputum conversion rate on culture, with the emergence of CAO syndrome, in our study, as well as with other authors, but also a statistically significant correlation with registered impaired lung function, expressed through the lung function parameters of interest, clearly show that the residual bronchial obstruction in active pulmonary TB, is an important clinical entity, which can be significant reason for the further health deterioration of cured TB patients (12, 14, 15).

6. CONCLUSION

The CAO syndrome is often a common initial manifestation of unrecognized COPD, which appears in the results of our investigation as a consequence and significant functional impairment of the respiratory system, in the field of extensive destruction of lung parenchyma and intense systemic inflammatory response, during the reparative processes in active TB, even in the absence of risk factors for COPD. Given the small number of studies of this problem in the literature, results of our investigation point to the fact that only microbiological cure of TB patients with underlying risks for disorders of lung function, is not sufficient and effective approach for prevention of their further potential health deterioration

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