IS SMOKING AN UNFAVORABLE PROGNOSTIC FACTOR FOR RHEUMATOID ARTHRITIS?

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ABSTRACT

Introduction: Smoking is the environmental factor that plays the most important role in the etiology of rheumatoid arthritis and the only one that can be changed. In rheumatoid arthritis patients, smoking results in erosive, rapidly progressive, poor therapeutic response. There are studies suggesting that auto antibodies (rheumatoid factor and anti citrullinated protein antibodies) production is triggered by exposure to smoking, thus contributing to rheumatoid arthritis.

Objectives: In this study we have proposed to analyze the effects of smoking on the rheumatoid arthritis.

Methods: We evaluated 285 patients with RA admitted to Department of Rheumatology, Clinical Emergency Hospital "St. Andrew", Constanța during January-December 2013. Demographics of patients and data on the onset and progression of RA were followed. We were particularly interested in the data related to the rheumatoid arthritis prognostic factors as they were established and published by the Romanian Rheumatology Society.

Conclusion: Smoking influences the onset of rheumatoid arthritis, the seropositivity, the presence of extraarticular manifestations, the acute phase reactants and the number of swollen joints. We can therefore conclude that smoking is an unfavorable prognostic factor for rheumatoid arthritis, influencing both the onset and its evolution.

Keywords: rheumatoid arthritis, smoking, unfavorable prognostic factor

Introduction

Rheumatoid arthritis (RA) is an important public health issue, both in that it has a worldwide prevalence of 1% (1), but also because it is a severe condition that evolves with significant, irreversible and precocious joints damages. The disease also has a strong social impact due to the motor disability it produces, which causes more than 50% of patients to end their professional activity in the first 5 years.

From the point of view of the pathogenic mechanism, rheumatoid arthritis is a prototype for immune-mediated inflammatory diseases. Genetic factors, autoimmunity, infectious

agents, oral contraceptives, smoking have been incriminated in the occurrence of rheumatoid arthritis. Smoking is the greatest environmental factor involved in the development of rheumatoid arthritis and the only one that can be changed.

Cigarette consumption is a significant risk factor for early rheumatoid arthritis through the role of pathogenic mechanisms in people with genetic predisposition (2) This role could be demonstrated by bronchoalveolar lavage. Thus, healthy smokers showed an increase in peptidylarginine deiminase 2 enzyme (PAD2) expression and citrulline (3), and in patients newly diagnosed with rheumatoid arthritis, a local increase in anti citrullinated protein

antibodies (Ac anti-CCP) was observed. (4)

Smoking induces citrulline, particularly in RA patients who have HLA class II histocompatibility antigen DR B1 common epitope alleles (5)

In rheumatoid arthritis patients, smoking results in erosive, rapidly progressive, poor therapeutic response. There are studies suggesting that rheumatoid factor (RF) production is triggered by exposure to smoking, thus contributing to rheumatoid arthritis. (6,7)

This study aims to analyze the effects of smoking on the rheumatoid arthritis prognostic factors.

Materials and methods

The study included 285 patients with RA (patients meeting the American Collage of Rheumatology –ACR - 1987 and The European League Against Rheumatism – EULAR - 2010 criteria) admitted to Department of Rheumatology, Clinical Emergency Hospital "St. Andrew", Constanța during January-December 2013.

Demographics of patients and data on the onset and progression of RA were followed. We were particularly interested in the data related to the rheumatoid arthritis prognostic factors as they were established and published by the Romanian Rheumatology Society (young age at onset, high titre of rheumatoid factor (RF), high titre of anti citrullinated protein antibodies (antiCCP), C-reactive protein (CRP) > 5xNormal Value and/or Erythrocyte Sedimentation Rate (ESR) > 50mm /h, Swollen Joint Count (SJC)> 5, presence of erosions and presence of extra articular manifestations) (8)

Subjects were divided into two population groups (smokers/non-smokers). The smokers group will have two subgroups: current smokers and current smokers. Also, the smoker status was observed at the onset of the condition.

Based on the information obtained, a database was created using the Microsoft Office Excel program. The statistical analysis was performed using MedCalc software and IBM SPSS Statistics 20 software. To highlight the differences between the two population groups, statistical tests were used. Statistically significant

$p < 0.05$ was considered statistically significant

Results

In the study group, consisting of 285 patients, as expected, the majority were women (85.6%), with an average age of 62.02 ± 11.72 years, with extreme extremes between 20 and 85 years. Most are urban (80.4%) and Caucasian (90.5%).

Regarding rheumatoid arthritis history, mean age at onset of disease was 51.15 ± 14.02 years. The duration of the disease was 11.28 ± 9.72 years, which made 89.5% of the patients have progressive RA. RF was present in 81% of patients and anti-CCP antibodies was positive in 70.3% of the 246 patients dosed.

Erosions were present in 218 patients (76.5%) and ankyloses in 98 (34.4%) of them. Extra articular manifestations were present in 194 (68%) of the patients, and the most frequent was rheumatoid nodules (24.9% - 71 patients).

Of the 285 patients with rheumatoid arthritis, 96 (33.68%) were smokers ever, 71 (24.92%) of them smoked at the onset of rheumatoid arthritis, and 34 (11.92%) were current smokers.

It followed if there was any difference between the age at onset in the two population groups. The results are in Table III and it is noted that smokers develop rheumatoid arthritis faster than non-smokers. Patients exposed to tobacco are diagnosed 4.56 years earlier than unexposed, and this difference is higher in the women's subgroup $\Delta t = 7.99$ years in the group of women that ever smoke and $\Delta t = 4.87$ years smoke on the onset)

The average of pack-year on smoker on onset was 17.17 ± 12.34 , and 81% of men that were smoking on the onset were great smokers (mean pack-year = 32.57 ± 12.47) compared with only 20% of women that were smoking on the onset (mean pack-year = 10.71 ± 18.66). There is a weak (positive) linear relationship between the onset age and the pack-year on the onset ($r = 0.3189$), but not between the age of the disease and the amount of tobacco consumed at the onset ($r = -0.1823$).

Correlations between unfavorable prognostic factors and smoker status have been made.

The presence of autoantibodies correlated with onset smoking status, with a statistically significant association with RF positive ($p = 0.0283$) and anti-CCP antibodies ($p = 0.0404$). In patients who are positive for both autoantibodies, this association is even stronger ($p=0,008$) and is also found in ever smoker patients ($p=0,0411$).

No significant correlation was found between erosion and tobacco exposure ($p = 0.8666$ for smokers ever, $p = 0.3858$ for onset smokers and $p = 0.2035$ for current smokers).

The presence of extra articular manifestations correlates with the current smoker status ($p = 0.0471$), and the correlation is even stronger between the presence of rheumatoid nodules and smoking exposure ($p = 0.0018$) and the onset of smoker at the onset ($p = 0,0004$).

Regarding the correlation of the smoking status and disease activity indicators ($ESR > 50\text{mm / h}$, $CRP > 2.5\text{mg / l}$, $SJC > 5$), statistically significant correlations were obtained both with the positive phase reactive reagents, but also with the number of inflamed joints.

Discussion

The demographic data of the patients in the studied group are compliant to the data that are found in the literature, as it is well known that rheumatoid arthritis is a disease that affects women in particular (represents 85.6% in our group) and the highest incidence is in the age group 55-64 years (average age in the study group was 62.02 years) (9).

Seropositivity was 81% for RF and 70.3% for antiCCP antibodies, a greater than the 70% reported for RF (10).

Most patients have erosions and ankyloses, the latter being characteristic of stage IV, advanced disease. The long history of illness (the average disease duration is 11.28 years) could explain the presence of these radiological changes.

Extra articular manifestations were reported in 68% of the patients analyzed, and the most frequent of these were simple chronic anemia and rheumatoid nodules. Their share is 40% in the literature (11). The difference can be explained by the patient's characteristics in our group (the majority of patients are seropositive

and with an old, progressive form of disease).

In patients with early disease, smoking is associated with the early onset of the disease (12). This finding is also noticeable in the study group, and smoker women develop rheumatoid arthritis even 8 years earlier than non-smokers.

The involvement of smoking in the onset of rheumatoid arthritis is of concern to specialists in recent years, all the more so since it started to discuss a preclinical phase of the rheumatoid arthritis, an early stage in rheumatoid arthritis evolution where the presence of autoantibodies, phase reactants acute and proinflammatory cytokines (13). It appears that autoantibodies are present in the serum 5 years before the first symptoms appear. (14). This observation is important in demonstrating the role of cigarette consumption in the evolution of rheumatoid arthritis, because in the analyzed group the percentage of seropositive smokers (90% for RF and 80% for antiCCP antibodies) is statistically significantly higher than non-smokers at the onset of seropositive (79% for RF and 67% for antiCCP antibodies).

Regarding the negative prognostic factors for rheumatoid arthritis, the presence of erosions does not correlate with our smoking exposure, but by analyzing the sublots we found a significantly higher proportion of them in current smokers' men. In fact, most studies do not suggest that smoking would influence radiological progression (12) although there are some who support this influence (15).

Extra-articular manifestations are associated with current smoker status, both in the whole lot and in the subgroup of women and Caucasians, taking into account the views of cohort analyzes made in other centers.(16, 17)

By evaluating the biological inflammation syndrome evidenced by ESR increase and CRP positivity, we can see that smokers ever have negative prognostic criteria higher than non-smokers ever, confirming data from specialist literature that states that smoking is associated with disease with activity (Tender Joint Count, Swelling Joint Count, Disease Activity Score with 28 joints – DAS28), and severe disease (15,18).

Supporting the same studies, the number of swollen joints above 5 is also associated

with smoking status (ever, at onset, current), especially Caucasian women.

Conclusions

Smoking influences the onset of rheumatoid arthritis, the seropositivity, the presence of extraarticular manifestations, the acute phase reactants and the number of swollen joints. We can therefore conclude that smoking is an unfavorable prognostic factor for rheumatoid arthritis, influencing both the onset and its evolution.

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