CLINICAL SCIENCE

SECONDARY SJOGREN'S SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Secondary Sjogren's syndrome (sSS) is a connective tissue disease characterized by xeropthalmia and xerostomia, associated with another autoimmune disease. The prevalence of sSS in patients with rheumatoid arthritis (RA) is different in different countries, but is assumed at 10% of all RA patients and 20% of these have sub-clinical manifestations. This is a large subpopulation of patients with RA, especially taking into account that the clinical implications of their coexistence are not well explored. Aims: To analyze the effects of sSS on RA, the association between this syndrome and disease activity and disease evolution, presence of serological and immunological markers, disease duration and quality of life in patients with RA. Material and methods: We examined 42 patients, at the age of 18 to 70 years, diagnosed according to the criteria for classification and diagnosis by EULAR (2010). Twenty patients were diagnosed with RA and sSS, and 22 patients with RA without sSS. The groups were comparable regarding age, sex and disease duration. We analyzed the incidence of sSS, association with age, sex, demographic data, disease duration, extraarticular manifestations, and serologic tests (positive RF, anti-CCP) were also made. Disease activity was assessed by disease activity score (DAS28) and quality of life by the health assessment questionnaire-disability index (HAQ-DI). The number of tender and swollen joints was assessed, as well as pain level by using the visual analogue scale (VAS), sedimentation rate (ESR), CRP, and immunological tests (SSA, SSB, antidsDNA, ANA, antiU1snRNP) were also made. Results: In the analyzed patients there was no statistically significant difference in ESR, CRP, DAS28, HAQ-DI, seropositivity of RF and anti-CCP and the presence of antidsDNA, ANA or antiU1snRNP and disease duration. Patients in the RA group had more tender, swollen joints and VAS. There was a statistically significant difference in SSA and SSB levels. There was no significant difference in the treatment of patients from both groups. Conclusion: There was no statistically significant difference in the level of disease activity and quality of life in patients with RA compared to sSS group.

КЛИНИЧКИ ИСТРАЖУВАЊА

СЕКУНДАРЕН СЈЕГРЕНОВ СИНДРОМ КАЈ ПАЦИЕНТИ СО РЕВМАТОИДЕН АРТРИТИС

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Извадок

Секундарниот Сјегренов синдром (сСС) претставува заболување на сврзното ткиво кое се карактеризира главно со појава на ксерофталмија и ксеростомија, во склоп на други автоимуни заболувања. Преваленцијата на сСС кај пациенти со ревматоиден артритис (РА) е различна во различни држави, но се претпоставува дека изнесува околу 10% од сите пациенти со РА, при што околу 20% од овие имаат супклинички манифестации. Ова претставува голема суппопулација на пациенти со РА, при што клиничките импликации на коегзистирањето на двете болести сèуште се недоволно испитани. Цели: Да се анализираат ефектите на појавата на сСС врз болеста, односно поврзаноста на овој синдром со активноста и еволутивноста на болеста, присуството на серолошки и имунолошки маркери, времетраењето на болеста и квалитетот на животот кај пациенти со РА. Материјал и методи: Беа испитани 42 пациенти на возраст од 18 до 70 години, дијагностицирани според критериумите на EULAR (2010). Дваесет пациенти беа со РА и сСС и 22 пациенти со РА без придружен сСС. Групите беа со слични карактеристики во однос на пол, возраст и времетраење на болеста. Беа анализирани: појавата на сСС и нејзината зависност од возраста и полот на пациентите, демографските податоци, траењето на болеста, присуството на вонзглобни манифестации, а беа направени и серолошки тестови (позитивниот RF, anti-CCP). Активноста на болеста беше анализирана преку индексот на активност на болест - DAS28 (Disease Activity Score 28), а квалитетот на живот на пациентите преку HAQ-DI (Health Assessment Questionnaire – Disability Index). Беше анализиран бројот на болни и отечени зглобови, VAS (визуелна аналогна скала на болка), седиментација на еритроцити (ESR), CRP, а беа направени и имунолошки тестови (SSA, SSB antidsDNA, ANA, antiU1snRNP) и по потреба други имунолошки и серолошки тестови). Резултати: Кај испитаните пациенти немаше статистички сигнификантна разлика во ESR, CRP, DAS28, HAQ-DI, серопозитивност кон RF или anti-CCP, како и присуството на antidsDNA, ANA или antiU1snRNP, како и траење на болеста. Пациентите во РА групата беа во поголем број, со повеќе отечени зглобови и повисока VAS. Постоеше статистички сигнификантна разлика во позитивноста на SSA и SSB антителата во двете групи. Немаше разлика во лекувањето на пациентите во двете групи. Заклучок: Не постои статистички сигнификантна разлика во нивото на активност на болеста и квалитетот на живот на пациентите со РА во споредба со оние со сСС.

Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disease which afflicts mainly the exocrine glands and is characterized by keratoconjunctivitis sicca and xerostomia[1]. The beginning of the disease is generally slow and patients at this time usually complain of generalized myalgia, arthralgia and fatigue.

Sjogren's syndrome is considered secondary when it is present in association with another autoimmune disease, even when SS was present before the "primary" disease. Lasarus et al. followed 114 patients with primary SS in a period of 10 years and showed that 13 of them had developed another autoimmune disease, which pointed out to a more generalized dysfunction of the immune system[2].

Secondary Sjogren's syndrome (sSS) is considered an extraarticular manifestation of rheumatoid arthritis (RA)[1]. The exact prevalence of sSS in patients with RA varies significantly, depending on the definition of sSS, duration of RA and the geographic region. The cumulative prevalence of sSS in patients with RA is 17% and 25% for duration of RA of 10 and 30 years correspondingly[3]. Another study from the UK confirms the association of sSS and RA according to disease duration[4], but a study from Norway doesn't show this[5]. This Norwegian study shows that the minimal prevalence of sSS in patients with RA is 7% and that there is no association between sSS and disease activity in RA. The same authors point out that there is a significant association between lower salivary production and disease activity in RA patients[5]. A study from Austria shows sSS prevalence of 22% in RA patients[6].

The relevance of sSS in patients with RA is clearly illustrated in the doubling of the risk of non-Hodgkin's lymphoma compared to patients with RA without sSS [7]. Some reports show increased mortality in patients with sSS[8,9].

The presence of sSS may point to a shorter life span in patients with RA and possibly higher disease activity. According to this, sicca symptoms should not be considered as irrelevant. It is important to explore whether sSS influences disease activity and the approach to treatment in patients with RA in everyday clinical practice.

The aims of our study were to examine the association of RA and SS in regard to disease activity, functional ability and quality of life, extraarticular manifestations, as well as possible correlation with serologic markers such as RF and anti-CCP and autoantibodies such as SSA, SSB, ANA, antidsDNA, antiU1snRNP. This should help us recommend a more optimal model for treatment and follow-up of patients with RA and sSS.

Materials and methods

This study was conducted at the University Clinic for Rheumatology in Skopje, North Macedonia. All patients were recruited and followed at this Clinic. We examined 42 patients, aged 18 to 70 years, who were previously diagnosed with RA and sSS, coming to the Clinic for a follow-up visit. All patients were informed about the goals of the study, and they could ask relevant questions.

After signing the informed consent, all the necessary procedures in the study were started.

Patients were divided into two groups, patients with RA and patients with RA and sSS. All patients were diagnosed according to the EULAR criteria for classification and diagnosis of RA and SS. The groups were comparable according to size, age and sex distribution.

Patients with other autoimmune diseases such as but not limited to systemic lupus, sarcoidosis, ankylosing spondylitis, Lyme disease etc. were excluded from the study. Similarly, patients with severe infections, history of irradiation of the neck or head, history of lymphoma or other malignant disease, or regular use of anticholinergics were excluded.

The analysis of RF and CRP were done on a biochemical analysis machine (BioSystems A15). Levels of anti-CCP and antiU1snRNP were determined by ELISA (Elisis Duo Human), while antidsDNA, SSA and SSB were done on Mindray MR-96A ELISA. The antinuclear antibodies (ANA) were analyzed by using immunofluorescence, on an Olympus CX31 microscope, by the same doctor certified for the use of this method.

After collecting data, disease activity was calculated by the use of DAS28-ESR scale. Quality of life was assessed with the HAQ-DI questionnaire. The average pain level was assessed by the patient marking the VAS scale incorporated in the HAQ-DI questionnaire. Disease activity and quality of life was compared between both groups.

All data was collected in digital tables and SPSS v19.1 was used for statistical analysis. Comparation between groups was done by Student's t-test and Chi-square tests. Correlation analysis was done by Pearson's analysis. P values <0.05 were considered statistically significant.

Results

We examined 42 patients, aged 18 to 70 years, with an average age of 61.22 years. Twenty-eight (66.67%) were women and 14 (13.33%) were men. The average disease duration of RA was 10.34 years and 34 patients (80.95%) had positive RF.

As shown in Table 1, there was no statistically significant difference in demographic, clinical and serologic characteristics between the groups. There was a statistically significant difference in levels of SSA and SSB, and ANA Hep2 positivity (which correlates to SSA and SSB levels), which was expected. These antibodies are specific for patients diagnosed with Sjogren's syndrome. There was no significant difference in the levels of antidsDNA and antiU1snRNP.

Table 1. Demographic, clinical, serologic and immunologic data

	Patients with RA and sSS (SD) n=20	Patients with RA (SD) (n=22)	P value
Duration of RA	10.45 (9.98)	10.23 (10.11)	NS
Age	62.12 (12.43)	60.33 (13.19)	NS
ESR (mm/1 hour)	14.82 (8.18)	20.21 (14.48)	NS
CRP (mg/l)	1.42 (5.99)	1.74 (7.89)	NS
Number of tender joints	0.89 (3.11)	0.32 (0.97)	NS
Number of swollen joints	2.33 (3.45)	1.31 (2.75)	NS
VAS (pain level inmm)	38.98 (27.34)	28.79 (22.91)	NS
DAS28-ESR	2.69 (0.97)	3.12 (1.19)	NS
Anti-CCP (U/ml)	127.33 (160.1)	138.21 (141.13)	NS
RF IgG (U/ml)	53.90 (44.2)	133.74 (220.12)	NS
Anti-dsDNA (U/ml)	56.18 (58.55)	72.34 (102.45)	NS
SSA (U/ml)	102.44 (29.19)	28.15 (34.1)	<0.05
SSB (U/ml)	88.23 (20.73)	26.67 (12.29)	<0.05
antiU1snRNP (U/ml)	26.12 (75.76)	28.47 (56.22)	NS
ANA Hep2 positivity	13	3	<0.05
HAQ-DI	0.89 (1.23)	0.94 (1.46)	NS

The value of RF IgG was higher in patients but without statistical significance. The number of tender and swollen joints, pain according to the VAS scale were higher in the sSS group, but this was also statistically insignificant. All patients were treated with a disease modifying anti-rheumatic drug (DMARD).

The comparison of disease activity of RA according to DAS28-ESR and the quality of life according to the HAQ-DI questionnaire showed no statistically significant difference.

Discussion

Secondary Sjogren's syndrome is a common extraarticular occurrence in patients with rheumatoid arthritis. This has beenshown in several studies, such as the one from Norway where 60.7% of the examined patients with RA complained of at least one symptom of dryness (mouth, eyes, trachea, etc.) [5]. One study from Turkey showed significantly less sicca symptoms (11.4%) in patients with RA than data from the UK, USA, but more present than information gathered in east Asia or Africa[10]. Haga et al. showed that 28% of patients with RA complained of at least one symptom of dryness, though sSS prevalence wasminimal, 3.6%[11]. The prevalence of sSS varies greatly, form 43% in Greece to 17% in patients with RA in Great Britain[12].

One study of patients with early arthritis[4] discovered an association between RA disease duration and the prevalence of sSS. As in the Norwegian study, our data did not support this notion.

Although sicca symptoms are considered to be difficult for patients with RA, serious complications are rare[13]. We still have to remain aware of data showing the association of sSS and the doubling of risk for non-Hodgkin's lymphoma, compared to patients with RA without sSS[7], as well as increased mortality[8,9]. There is a suggestion that sSS is associated with higher disease activity in patients with RA 4 and there is a correlation between lower saliva production and higher RA disease activity[5]. We, like Haga et al. did not find an association between DAS28-ESR and sSS. There were more tender and swollen joints in patients with sSS, but it was not statistically significant.

The value of RF was higher in the RA group, but this was statistically insignificant. All patients were treated with DMARDs, but no patients in the sSS group were treated with a biologic drug.

The number of patients with sSS in this study was small(n=20), and hence, there was a high standard deviation and it wa smore difficult to show statistically significant differences. We assume that the increased number of tender and swollen joints in patients with sSS to be a result of the stated statistical weakness, and not showing more severe disease activity (DAS28-ESR had no statistically significant difference between the groups).

We believe that there may be an increased disease activity in the RA group of patients. This is based on the higher levels of the inflammatory markers, HAQ-DI score, as well as presence of patients treated with biologics which is a sign of intransigent and severe disease. With the increase of the number of examined patients, these differences may be better elaborated and the statistical significance may increase.

In conclusion, we found no statistically significant difference in disease activity or quality of life in patients with RA in comparison with those with sSS.

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