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COMPARATIVE ANALYSIS OF SERONEGATIVE AND SEROPOSITIVE RHEUMATOID ARTHRITIS REGARDING SOME EPIDEMIOLOGICAL AND ANAMNESTIC CHARACTERISTICS

USPOREDNA ANALIZA SERONEGATIVNOG I SEROPOZITIVNOG REUMATOIDNOG ARTRITISA U ODNOSU NA NEKE EPIDEMIOLOŠKE I ANAMNESTIČKE ZNAČAJKE

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Summary

Classifying patients into two subsets of the disease - seronegative RA and seropositive RA - has been the subject of many studies which aim to clarify this phenomenon - without any conclusive or acceptable answer so far. The aim of this prospective study was to establish a scientific comparative analysis between seronegative and seropositive rheumatoid arthritis (RA) regarding some epidemiological and anamnestic characteristics. The studied group consisted of seronegative patients with titers lower than 1:64 as defined by Rose-Waaler test, while the control group consisted of seropositive patients with titers of 1:64 or higher. All patients belonged to 2nd and 3rd functional class according to the ARA criteria, were between 25-60 years of age (Xb=49,96), with disease duration between 1-27 years (Xb=6,41). Education, residence, economic and living conditions did not show any significant statistical difference regarding serostatus. Familial clustering of RA confirmed higher susceptibility in the seropositive group (χ^2=7,02; p<0,01). In both subsets banal diseases, psychic and physical trauma, weakness, and numbness of hands and legs dominated, without any statistical difference regarding serostatus. Some differences between groups regarding sex were noticed, but were not statistically significant, except regarding physical trauma, which was more present in seronegative females (χ^2=8,05; p<0,01).

Key words

rheumatoid arthritis, seropositive, seronegative, epidemiology, anamnesis

Sažetak

Klasifikacija bolesnika s reumatoidnim artritisom (RA) u dvije skupine - seronegativni RA i seropozitivni RA - predmet je mnogih dosadašnjih istraživanja. U ovome prospektivnom istraživanju provedena je usporedna analiza seronegativnog i seropozitivnog reumatoidnog artritisa u odnosu na neke epidemiološke i anamnestičke karakteristike. Ispitivanu skupinu činili su bolesnici sa seronegativnim RA s titrom manjim od 1:64 određenim pomoću Waaler-Roseova testa, dok su kontrolnu skupinu činili bolesnici sa seropozitivnim RA s titrom 1:64 ili višim. Svi ispitanici su pripadali II. I III. funkcijskom razredu (ARA), bili su životne dobi između 25-60 godina (Xb=49,96) s trajanjem bolesti 1-27 godina (Xb=6,41). Edukacija, mjesto boravka, ekonomski i životni uvjeti nisu pokazali znatnu statističku razliku u odnosu na serološki status. U bliskih rođaka RA je bio češće prisutan u seropozitivnoj skupini (χ^2=7,02; p<0,01). U obje skupine dominirale su tzv. banalne bolesti, psihičke i fizičke traume, malaksalost, ali bez istaknute statističke razlike u odnosu na serološ-

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ki status. Nađene su određene razlike između skupina u pogledu spola, ali nisu bile statistički značajne, osim kod fizičkih trauma koje su bile češće prisutne u seronegativnih žena (χ^2=8,05; p<0,01).

Ključne riječi

reumatoidni artritis, seropozitivan, seronegativan, epidemiologija, anamneza

Introduction

Rheumatoid arthritis is the frequent chronic autoimmune inflammatory disease, a mainly multisystemic arthropathy, with a complex, multifactorial and unknown etiology, affecting synovial tissue of the peripheral joints and extra-articular structures. The disease presents a wide spectre of clinical phenotypes of progressive, unspecific and destructive polyarthritis, which leads to irreversible joint damage, deformities and disability [1,2,3,4,5,6,7,8].

Although the etiopathogenesis of RA is unknown, the majority of scientists have supported the immunology based theory after the discovery of the rheumatoid factor (RF) [9,10,11]. RF is an antiimmunoglobuline with a course against Fc fragment of IgG humane molecule [12,13]. It is not a pathognomonic sign of RA [14] because it can be present in patients with various inflammatory disorders [15], as well as in 5%-8% of healthy population. However, it can be considered a parameter of immunological activity [16]. RF occurs more frequently in healthy women than in healthy men [17], and is more frequently present in urban than rural population [18,19,20]. People without symptoms with RF persistently increased are more susceptible to develop RA [19,20]. In some studies RF generation was associated with the presence of HLA-DR4 and DRB1 [21]. RF can be in different immunoglobuline classes (G,A,D and E) defined by ELISA [3,10]. Agglutination-based test methods (Rose-Waaler and Latex tests), which prove only the presence of RFIgM, have recently been more frequently used [22]. RF is present in 70%-80% of patients with RA, where the disease is defined as a seropositive arthropathy [23].

External factors are of particular importance and were explored in many studies [24]. Patients with RA often suffer from depression, assumedly as a consequence of the disease [25]. Clinical, laboratory and pathohistological signs indicate infective pathology [26], but efforts to discover the cause have so far ended without success [27]. Patients with AR who smoke are mostly seropositive, associated with DBR1*0401[28,29,30,31,32].

Purpose

The aim of this prospective study was to establish a scientific comparative analysis between seronegative and seropositive rheumatoid arthritis (RA) regarding some epidemiological and anamnestic characteristics. Effort was made to contribute to the clarification of the existing dilemma in literature: are these forms variations of the same disease, or are they two different diseases. This was the first such study among Kosovo population.

Patients and Methods

In this prospective study, conducted between 1991-2004, 250 patients with seronegative and seropositive RA were examined at the Clinic for Sport Medicine in Pristina and at internal medicine facilities in Kosovo.

Patients had the classic form of RA, and all fulfilled the ARA criteria [33]. The test group consisted of 125 seronegative RA patients (93 female, 32 male), with titers lower than 1:64 as defined by Rose-Waaler test. The control group consisted of 125 seropositive RA patients (93 female, 32 male), with titers of 1:64 or higher. Patients all belonged to the 2nd and 3rd functional class (ARA), and were between 25-60 years of age. The duration of the disease was 1-27 years. Socio-economic data was explored: educational level (low, middle and high), economic (poor, medium and good), living conditions (humid or not), and area of residence (village, city). Within anamnestic data familial anamneses, potential provocative factors at the beginning of the disease, prodromale symptoms foregoing the disease (supposed to appear six months or more before the clarified status) were recorded.

Statistical parameters used for presentation of the results: structure, prevalence, arithmetic average (Xb), standard deviation (SD), variation coefficient (CV%) and variation interval (Rmax-Rmin). T test and χ^2 test were used to determine differences between factors or features. Probability level was expressed by p<0,01 and p<0,05.

Results

Approximately two thirds of the total number of patients were dominated by uneducated (39 (31,2%) seronegative, 41 (32,8%) seropositive) and low-educated patients (40 (32%) seronegative, 47 (37,6%) seropositive). Majority had medium living conditions (52 (41,6%) seronegative, 46 (36,8%) seropositive). More than half came from urban areas (70 (56%) seronegative, 65 (52%) seropositive). Patients of both groups were living in conditions that were not humid (116 (92,8%) seronegative, 114 (91,2%) seropositive). Above mentioned

Table 1. **Socio-economic parameters regarding sero-status and sex**
Tablica 1. **Socioekonomski parametri u odnosu na serološki status i spol**

Parameter	Modality	Women RASN N	Women RASN %	Women RASP N	Women RASP %	Men RASN N	Men RASN %	Men RASP N	Men RASP %	Total RASN N	Total RASN %	Total RASP N	Total RASP %
Education	uneducated	33	35,5	36	38,7	6	18,8	5	15,6	39	31,2	41	32,8
	low	31	33,3	31	33,3	9	28,1	16	50,0	40	32,0	47	37,6
	middle	20	21,5	20	21,5	15	46,9	10	31,3	35	28,0	30	24,0
	high	9	9,7	6	6,5	2	6,2	1	3,1	11	8,8	7	5,6
	Test	$X^2=0,73$		P>0,05		$X^2=0,338$		P>0,05		$X^2=1,89$		P>0,05	
Economic conditions	poor	30	32,3	29	31,2	7	21,9	12	37,5	37	29,6	41	32,8
	medium	35	37,6	32	34,4	17	53,1	14	43,8	52	41,6	46	36,8
	good	28	30,1	32	34,4	8	25	6	18,8	36	28,8	38	30,4
	Test	$X^2=0,42$		P>0,05		$X^2=1,89$		P>0,05		$X^2=0,63$		P>0,05	
Residence	vilage	42	45,2	39	41,9	13	40,6	21	65,6	55	44,0	60	48,0
	city	51	54,8	54	58,1	19	59,4	11	34,4	70	56,0	65	52,0
	Test	$X^2=0,09$		P>0,05		$X^2=3,08$		P>0,05		$X^2=0,26$		P>0,05	
Living conditions	humid	6	6,5	8	8,6	3	9,38	3	9,4	9	7,2	11	8,8
	not humid	87	93,5	85	91,4	29	90,6	29	90,6	116	92,8	114	91,2
	Test	$X^2=0,78$		P>0,05		$X^2=0,00$		P>0,05		$X^2=0,05$		P>0,05	

Table 2. **Familial anamnesis parameters regarding sero-status and sex**
Tablica 2. **Parametri obiteljske anamneze u odnosu na serološki status i spol**

Parameter	Modality	Women RASN N	Women RASN %	Women RASP N	Women RASP %	Men RASN N	Men RASN %	Men RASP N	Men RASP %	Total RASN N	Total RASN %	Total RASP N	Total RASP %
Familial anamnesis	no	81	87,1	70	75,3	27	84,4	20	62,5	108	86,4	90	72,0
	yes	12	12,9	23	24,7	5	15,6	12	37,5	17	13,6	35	28,0
	Test	$X^2=3,52$		P>0,05		$X^2=2,88$		P>0,05		$X^2=7,02$		P<0,01	

parameters did not show significant statistical difference regarding sero-status and sex (table 1).

Familial clustering of RA confirmed higher susceptibility in the seropositive group - 35 (28%), than in seronegative - 17 (13,6%), with significant statistical difference ($X^2=7,02$; p<0,01). Among female patients with positive familial anamnesis dominated seropositive - 23 (24,7%), compared to seronegative - 12 (12,9%). Among male patients with positive familial anamnesis it was the same case - 12 (37,5%) seropositive, versus 5 (15,6%) seronegative, but without significant statistical difference (table 2).

More frequent were banal diseases (44 (35,2%) seronegative, 39 (31,2%) seropositive), and psychic trauma (39 (31,2%) seronegative, 34 (27,2%) seropositive) in both groups, but no statistical significance was found (table 3). According to sex, psychic and physical trauma dominated in seronegative women and seropositive men, but significant statistical difference was found in the physical trauma in seronegative women 17 (18,3%) ($X^2=8,05$; p<0,01). In both subsets dominated weakness (91 (72,8%) seronegative, 92 (73,6%) seropositive) and hands and legs numbness (88 (70,4%) seronegative, 80 (64%) seropositive), without any statistical difference regarding sero-status (table 4). There were some differences between groups regarding sex, but not statistically significant.

Discussion

Huge amount of information regarding the role of genetic factors in RA has been gathered, but not precisely clarified yet. Different mechanisms are involved in generating and proliferating process of HLA-DR (34,35). The common method of exploring the role of genetic factors in RA is the determination of the frequency of the onset of the disease in monozygotic twins, which usually appears in 30% of cases, and 5% in dizygotic twins (36,37).

Analyzing our familial anamnestic data, we found that among related persons RA was more present in seropositive (28%) than in seronegative (13,6%) subset, and this difference was statistically significant ($X^2=7,02$; p<0,01), without difference in sex. This leads to conclusion that RA seronegative patients are less influenced by familial component (38), which is contrary to Conway SC et al. (39), who did not find a difference between se-

Table 3. **Type and frequency of potential provocative factors regarding sero-status and sex**
Tablica 3. **Vrsta i učestalost mogućih uzročnih činitelja u odnosu na serološki status i spol**

Potential provocative factors	Women						Men						Total					
	RASN			RASP			RASN			RASP			RASN			RASP		
	N	%	X^2	N	%	P	N	%	X^2	N	%	P	N	%	X^2	N	%	P
Psychic trauma	33	35,5	0,60	27	29,0	>0,05	6	18,8	0,08	7	21,9	>0,05	39	31,2	0,34	34	27,2	>0,05
Physical trauma	17	18,3	8,05	4	4,3	<0,01	9	28,1	1,50	15	46,9	>0,05	26	20,8	1,09	19	15,2	>0,05
Banal diseases	35	37,6	0,78	28	30,1	>0,05	9	28,1	0,20	11	34,4	>0,05	44	35,2	0,30	39	31,2	>0,05
Birth	16	17,2	0,03	17	18,3	>0,05							16	12,8		17	13,6	
Menopause	10	10,8	0,18	12	12,9	>0,05							10	8,0		12	9,6	

Table 4. **Prodromal symptoms of RA regarding sero-status and sex**
Tablica 4. **Prodromalni simptomi RA u odnosu na serološki status i spol**

Prodromal symptoms	Women						Men						Total					
	RASN			RASP			RASN			RASP			RASN			RASP		
	N	%	X^2	N	%	P	N	%	X^2	N	%	P	N	%	X^2	N	%	P
Weakness	75	80,6	0,45	67	72,0	>0,05	16	50,0	1,98	25	78,1	>0,05	91	72,8	0,01	92	73,6	>0,05
Loss of appetite	40	43,0	0,21	36	38,7	>0,05	7	21,9	0,25	9	28,1	>0,05	47	37,6	0,04	45	36,0	>0,05
Weight loss	20	21,5	0,00	20	21,5	>0,05	3	9,4	0,25	3	9,4	>0,05	23	18,4	0,00	23	18,4	>0,05
Psychical disorders	32	34,4	0,89	40	43,0	>0,05	12	37,5	2,88	5	15,6	>0,05	44	35,2	0,01	45	36,0	>0,05
Diverse vasomotoric	27	29,0	0,32	23	24,7	>0,05	4	12,5	0,82	7	21,9	>0,05	31	24,8	0,02	30	24,0	>0,05
Raynaud's phenomenon	5	5,4	0,09	6	6,5	>0,05	1	3,1	0,00	1	3,1	>0,05	6	4,8	0,08	7	5,6	>0,05
Undifferentiated pains	46	49,5	0,64	54	58,1	>0,05	26	81,3	2,38	16	50,0	>0,05	72	57,6	0,02	70	56,0	>0,05
Hand numbness	69	74,2	0,27	63	67,7	>0,05	19	59,4	0,11	17	53,1	>0,05	88	70,4	0,38	80	64,0	>0,05

ropositive and seronegative subsets regarding familial anamnesis.

In recent immunological studies there was no agreement regarding this phenomenon. Singal DP. et al. (40) and Lang B. et al. (41) found higher values of RFIgM in RA patients with antigen HLA-DR4 and DR1. RA patients who belonged to subtype groups DR4 and DBR1, particularly to genotype DBR1*0401/0404, were more likely to become seropositive with a progressive and heavy disease (42,43,44,45,46,47,48,49). Ploski R. et al. (50) was of the same opinion, and has noticed that DBR1*0101 can be accompanied with a light seropositive RA, maybe with seronegative RA as well, but not with well-established RA.

Above mentioned authors have confirmed DR4 accompanying seropositive RA - but studies of seronegative RA, even limited, showed contradictory results. In this sense al-Jarallah KF. et al. (51) and Silman A. et al. (53) affirmed that because seropositive and seronegative RA are accompanied by DR4, these two forms likely have the same imunogenetic base.

More radical was Husby G. (53) - who found that DR4 in RA seronegative subset was accompanied by the more destructive disease. Vehe RK. et al. (54) confirmed that these antigens are prevalent in the patients with erosive RA, regardless of the RF status.

Regarding the dilemma - if seropositive and seronegative RA belong to the same spectrum of the disease - Calin A. et al. (55) confirmed that the frequency of DR4 was positive in 69% of cases with seropositive RA and in 60% of cases with seronegative RA. In both groups DR4 was accompanied with destructive RA. Dieude P. et al. (56) found that in familial RA there is an interaction between receptor I of TNF (TNF-I) and (TNF-II), locus TNFR1 and TNFR2, which can help in genetic predictions of RA.

Even if the role of environmental factors was important (57,58,59,

60), our data did not show any significant difference regarding sero-status and sex. The relation between stress and RA remains unclear and undefined (61). Many authors assert that within existing predisposition, stress, trauma or surgical intervention can provoke or precipitate appearance of RA, but there is no scientific confirmation yet (62,63,64,65).

In patients with RA, 9-15% of cases cause disability due to psychic state (van der Heide A. et al. (66). Herrmann M. et al. (65), Zaitseva TV. (67) have found hypochondriacs, neurasthenics, apathy, aggressiveness and rigidity of a psychic profile in patients with RA). Presence of stress before the onset of the disease, according to Mur E. et al. (68) and Kjeldsen KJ. (69), was more frequently found in seronegative than in seropositive patients, which is in concordance with our results. However, we did not find relevant statistical difference. We found statistical difference in higher presence of physical trauma among female seronegative patients (χ^2=8,05; p<0,01). As far as Gunther V. et al. (70) has observed, seronegative patients are strong-willed in controlling stress situations. On the other hand Conway SC. et al. (71) did not find differences regarding sero-status. Prodromal symptoms in the literature are estimated sporadically and without a prediction component, but are useful for early diagnosis of RA, and could help as a parameter of the activity of the disease (33,72). In our data we found approximately equal presence of prodromal symptoms in both subsets.

Conclusions

Education, residence, economic and living conditions did not show any significant statistical difference regarding sero-status. Familial clustering of RA confirmed higher susceptibility in the seropositive group.

Psychic and physical trauma was more present in seronegative females. Prodromal symptoms were equally distributed in both subsets. Differences regarding sex, with some exceptions, were not significant.

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