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Course and prognosis in seropositive and seronegative rheumatoid arthritis

Tijek i prognoza seropozitivnog i seronegativnog reumatoidnog artritisa

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Summary

Long since it have been suggested that a subpopulation of patients with rheumatoid arthritis (RA), diagnosed with negative rheumatoid factor (RF) tests, represents a clinical entity quite distinct from that of seropositive rheumatoid arthritis. The aim of the study was to establish a scientific comparative analysis between RA seronegative and seropositive, regarding course and prognoses of the disease. Two hundred fifty patients with rheumatoid arthritis according to the (American College of Rheumatology) criteria were retrospectively studied by analysis the course and prognoses of disease. All examinees were between 25-60 years of age ($X_b=49.9$, $SD=10.3$) with disease duration between 1-27 years ($X_{box}=6.41$, $SD=6.47$). Course of the disease with "remissions and ex-

acerbations", progressive continual course and bad prognoses, were more presented in seropositive group of patients. Partial remission was more common in seronegative patients but according to serostatus and gender has not shown statistically significant difference. Duration of the disease was a specific prognostic sign for both subsets [($r=0.32$, $p<0.01$) seronegative, ($r=0.22$, $p<0.05$) seropositive], while age was only a specific prognostic sign for the seropositive subset [($r=0.01$, $p>0.05$) seronegative, ($r=0.18$, $p<0.05$) seropositive]. Seropositive and seronegative RA distinguish in course and prognostic feature, but not enough to differentiate them in two different forms of the disease. Regarding the sero-status, differences within sex, with some exceptions, are not relevant.

Keywords

rheumatoid arthritis, seropositive, seronegative, course, prognoses

Sažetak

Već odavno je sugerirano da subpopulacija bolesnika s reumatoidnim artritismom (RA), diagnosticirana s negativnim testom za reumatoidni faktor (RF), predstavlja klinički entitet sasvim različit od populacije sa seropozitivnim reumatoidnim artritismom. Da bi se uspostavila znanstvena komparativna analiza između seronegativnog i seropozitivnog reumatoidnog artritisa (RA), u odnosu na tijek i prognozi bolesti, dvjesto pedeset bolesnika s reumatoidnim artritismom u skladu s kriterijima ACR (American College of Rheumatology), retrospektivno su ispitivani analizom tijeka i prognoze bolesti. Svi ispitanici su bili između 25-60 godina ($X_b=49,9$, $SD=10,3$) s trajanjem bolesti od 1-27 godina ($X_b=6,41$, $SD=6,47$). Tijek bolesti s "remisijama i egzacerbacijama", kontinuu-

alno progresivni tijek i loša prognoza, bile su prisutnije u seropozitivnoj skupini bolesnika. Djelomična remisija je bila prisutnija u seronegativnoj skupini bolesnika, mada u odnosu na serostatus i spol nije predstavljala statistički značajnu razliku. Dužina trajanja bolesti se pokazala kao specifični prognostički znak za obe skupine [($r=0,32$, $p<0,01$) seronegativni, ($r=0,22$, $p<0,05$) seropozitivni], dok se pokazao specifični prognostički znak samo za seropozitivnu skupinu [($r=0,01$, $p>0,05$) seronegativni, ($r=0,18$, $p<0,05$) seropozitivni]. Seropozitivni i seronegativni RA se razlikuju po pitanju karakteristika tijeka i prognoze, ali ne dovoljno da bi ih razlikovali kao dvije različite vrste iste bolesti. U odnosu na spol, osim izvjesnih izuzetaka, razlike nisu značajne.

Ključne riječi

reumatoidni artritis, seropozitivni, seronegativni, tok, prognoza

Introduction

Rheumatoid arthritis is an auto-immune disorder which diagnosis is based on clinical, radiological and biological criteria. Only rheumatoid factor is actually considered as biological factor among recognized diagnostical criteria despite its weak sensibility and specificity rates (1). Course of the disease is variable and unpredictable, because it may be followed by spontaneous remission, especially at the beginning of the disease (2,3) but, may have also exacerbations during its entire course (4,5). Nearly 20-25 % of patients have the onset of the disease associated with progressive continuous course, while 50-60 % of patients experience periods of very active disease and remission.

According to some authors, there are several factors that predict bad prognosis: disease activity, old age, early attack in MTP joints, disease duration, RF high titer,

presence of ANA, female gender, vasculitis, early erosive damages, PCR high levels, poliarticular symmetric onset, rheumatoid nodules and tissue type DR1, DR4, DRB1 (2,6,7,8,9,10,11,12,13,14).

When the disease is always active during the first year, remission appears very rarely (15). American Rheumatism Association (ARA) in the year 1981 proposed remission RA criteria which are Paulus modified criteria (16). Predictors of poorer treatment response and thus a worse prognosis include female gender, being a smoker, autoantibody positivity, high baseline disease activity and co-morbidities such as depression (17,18,19)

Contemporary developments in drug and surgical methods have improved long-term outcomes of the disease, but RA remains a serious disease. Therefore, studies for prognostic signs would be of great importance to (20).

Aim

The aim of this paper is to establish a scientific comparative analysis between rheumatoid arthritis (RA) sero-

negative and seropositive, regarding course and prognoses of the disease.

Examinees and methods

A total of 250 patients with Rheumatoid Arthritis were included in the study as they meet the American College of Rheumatology ACR (1987) revised diagnostic criteria (20). Patients were retrospectively reviewed by analysis the course and prognoses of disease. The studied group consisted of 125 (93 female, 32 male) seronegative patients with titers lower than 1/64 as defined

by Rose-Waaler test, whereas the control group consisted of 125 (93 female, 32 male) seropositive patients with titers of 1/64 or higher. Patients who belonged to 2nd and 3rd functional class (ARA) are taken into consideration. Disease duration was between 1-27 years ($X_b=6.41$) (seronegative $X_b=6.4$, $SD=5.9$, seropositive $X_b=6.3$, $SD=6.9$). Their age ranged from 25 to 60 years

($X_b=49.9$) (seronegative $X_b=46.6$, $SD=10.3$, seropositive $X_b=47.3$, $SD=10.4$).

We used ARA criteria (1981) to define remission which are modifications of the criteria of Paulus (16). In case of exacerbation of the rheumatoid process, patients were treated same as during first visit at clinic. Course and prognosis of the disease in our study were predicted by some relevant parameters such as gender, age, function-

al status, education, onset and duration of disease. The structure, prevalence, arithmetic average (X_b), standard deviation (SD), variation coefficient ($CV\%$) and variation interval ($R_{max}-R_{min}$) were used for the presentation of the results. Probability level was expressed by $p<0.01$ and $p<0.05$. The correlation between the prognosis and duration of RA (in years), prognosis and age of RA, regarding serostatus was measured by "Point-biserial" correlation.

Results

Table 1. The clinical course of RA regarding serostatus and sex.*(exacerbation)

Clinical course of the disease	Female				Male				Total			
	SNRA		SPRA		SNRA		SPRA		SNRA		SPRA	
	N	%	N	%	N	%	N	%	N	%	N	%
Remission and e*	40	43.0	50	53.8	20	62.5	13	40.6	60	48.0	63	50.4
Continual progressive	21	22.6	25	26.9	4	12.5	8	25.0	25	20.0	33	26.4
Partial remission	30	32.3	18	19.4	6	18.8	11	34.4	36	28.8	29	23.2
Complete remission	2	2.2			2	6.3			4	3.2		
Test	$X^2=5.38$		$P>0.05$		$X^2=3.29$		$P>0.05$		$X^2=2.93$		$P>0.05$	

Course of the disease by flares (exacerbation) and remissions (table 1) was almost equally spread in both groups [60 (48%) seronegative, 63 (50.4%) seropositive].

Progressive continual course was more present in seropositive group of patients 33 (26.4%) than in seronegative group 25 (20%), whereas partial remission was more common in seronegative patients 36 (28.8%) than in seropositive 29 (23.2%).

Seropositive women experienced more often course characterized by exacerbation and remissions (43%:53.8%) and continuous progressive disease course (22.6%:26.9%), while partial remission was more common in the seronegative females (32.3%:19.4%).

Seropositive males dominated with continuous progressive disease course (12.5%:25%) and with partial remissions (18.8%:34.4%), while course characterized by exacerbation and remissions (62.5%:40.6%) was more present in seronegative males (62.5%:40.6%).

Differences regarding serostatus and gender have not shown any statistically significant difference.

Poor prognoses were found in about two-thirds of all the examinees (table 2). Seropositive patients experienced more often poor prognosis 97 (77.6%) than seronegative patients 85 (68%).

Both seropositive man 24 (75%) and woman 73 (78.5%) were more often associated with poor prognosis than seronegative man 23 (71.9%) and women 62 (66.7%). Differences according serostatus and gender have not shown any statistically significant difference.

Poor prognosis (table 3) is more often confirmed at intervals of disease duration of more than 10 years, 24 (88.9%) compared with the intervals of 1 to 10 years, 61 (62.2%).

Calculated the correlation coefficient between these parameters has resulted as high and positive ($r=0.32$, $p<0.01$).

Similar records were found is seropositive subset. Appearance of poor prognosis was higher at intervals of disease duration of more than 10 years, 79 (75.2%), compared with the intervals of 1 to 10 years, 18 (90%), associated by high correlation coefficient ($r=0.22$,

Table 2. Prognosis of RA regarding serostatus and sex

Sex	Sero-status	Prognosis of RA					
		Poor			Good		
		N	%	Test	N	%	Test
Female	SNRA	62	66.7	$X^2=0.90$	31	33.3	$X^2=2.37$
	SPRA	73	78.5	$P>0.05$	20	21.5	$P>0.05$
Male	SNRA	23	71.9	$X^2=0.02$	9	28.1	$X^2=0.06$
	SPRA	24	75.0	$P>0.05$	8	25.0	$P>0.05$
Total	SNRA	85	68.0	$X^2=0.79$	40	32.0	$X^2=2.12$
	SPRA	97	77.6	$P>0.05$	28	22.4	$P>0.05$

Table 3. Correlation between prognosis and duration of RA (in years), regarding serostatus

Duration of RA	SNRA				SPRA			
	Poor		Good		Poor		Good	
	N	%	N	%	N	%	N	%
1-10	61	62.2	37	37.8	79	75.2	26	24.8
>10	24	88.9	3	11.1	18	90.0	2	10.0
Total	85	68.0	40	32.0	97	77.6	28	22.4
Correlation	$r=0.32$		$p<0.01$		$r=0.22$		$p<0.05$	

Table 4. Correlation between prognosis and age of RA, regarding serostatus

Age	SNRA				SPRA			
	Poor		Good		Poor		Good	
	N	%	N	%	N	%	N	%
25-34	15	17.6	6	15.0	11	11.3	7	25.0
35-44	11	12.9	9	22.5	18	18.6	6	21.4
45-54	34	40.0	12	30.0	31	32.0	9	32.1
55-60	25	29.4	13	32.5	37	38.1	6	21.4
Correlation	r=0.01		P>0.05		r=0.18		P<0.05	

p<0.05). Results showed that the longer the duration of illness, the more frequent the appearance of poor prognosis.

Discussion

The prognosis for the patient with newly diagnosed rheumatoid arthritis (RA) has dramatically changed over the last two decades (21,22). Remission has become a realistic goal in the management of RA, particularly in early disease (23). According to Van Schaardenburg D. et al. (24), the retrospective follow up study in a sample of adult patients with RA reports more disease activity in seropositive patients.

While, Knijff DE. et al. (25) consider RF as disease activity parameter in patients with RA and there is a constant relation between disease activity and radiological damages, on the other hand, Schmidt KL. (26) thinks that there is no correlation between disease activity and RF. There are patients with severe progredient progress of the disease, with low titers of RF and vice versa.

Similarly it was found by a survey conducted in 1000 patients with RA; the detection of rheumatoid factors should be considered useless in predicting the course of disease as long as titers remain stable (27), while elevated PCR or ERS levels can be considered more helpful in this regard. Approximately in two thirds of all of our examinees was found poor prognosis, although more pronounced in seropositive but not at the level of statistical significance.

Our observations are related to the data of other authors, that seropositivity leads to a poor prognosis of RA (13,20,28,29,30,31,32). In our data we found that the duration of the disease is specific prognostic sign for patients of both groups, and age only for seropositive patients. These findings do not match those of Choy EH. et al. (13), who as nonspecific prognostic sign consider age and duration of illness, whereas the presence of early erosive changes, the higher titer of RF, high levels of PCR and high values of disease activity as specific signs.

In seronegative subset was recorded a tendency of increasing appearance of poor prognosis according to age, but with a high variability (table 4). The frequent appearance of poor prognosis, was amongst the oldest age groups [45 to 54 presence 34 (40%), 55 to 60 presence 25 (29.4%)] and no correlation was found between these parameters ($r = 0.01$, $p > 0.05$).

In seropositive subset, increasing rate of poor prognoses was ongoing continual, and also more pronounced in old age [31 (32.0%) in age group 25 to 34, and 37 (38.1%) in age group 55 to 60.

In this case, the estimated correlation coefficient is high and positive ($r = 0.18$, $p < 0.05$) which means that, with increasing age increases the chance of a poor outcome (increases the possibility of the appearance of poor prognosis).

Yamada A. (12) findings associated with duration of disease are consistent with our data, but he has found that to predict poor prognosis in early stage of AR there are several other factors such as disease activity ERS, PCR, high RF titers, male gender and vaskulitis. With these estimates agrees Combe et al. (19) and Scott DL. et al. (29).

According to Masi AT. et al. (33) the following entry factors were found to correlate significantly with a better outcome: maleness, acute onset under age 30, less swollen upper joints, and negative RF. On the other hand, Mozaires B. (34), above mentioned factors does not consider as valid prognostic indicators. Jansen LM. et al. (35), Bas S. et al. (36) claim that the prognostic values of anti-PCC, can predict milder seronegative form of the disease.

As far as Konečni J. et al. (37) have confirmed that when seropositive patients turn into seronegative have better prognosis than those that remain always seropositive, while Tuomi T. et al. (38) have opposite opinion about this issue.

Our data, in terms of age and functional disability, are in complete agreement with the findings of Sherrer YS. et al. (39), Schmidt M. et al. (40) and partly with those of Smedstad LM. et al. (41), who, in their study on 706 RA patients, with disease duration of 4 or <4 years, have found that sex, ERS and disease duration have correlated with functional disability while, for age, education and FR have not found a statistically significant difference.

The same authors emphasize that in cases of early onset arthritis, female gender correlates significantly with functional disability but not with FR. However, Papadopoulos IA. et al. (42), van Schaardenburg D. et al. (24), van Zeben D. et al. (43) claim that seropositive patients end up with the most limited functional abilities.

Conclusion

Course with “remissions and exacerbations”, progressive continual course and bad prognoses, are more present in seropositive group of patients, without significance re-

garding serostatus. Duration of the disease is a specific prognostic sign for both subsets, while age is only a specific prognostic sign for the seropositive.

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