Early rheumatoid arthritis: Does gender influence disease expression?

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Abstract

Objective

To investigate whether gender is an independent factor associated with disease expression in early rheumatoid arthritis (RA) patients.

Methods

438 patients with early RA (disease duration less than one year) were studied. They all were patients with early RA who presented at the Rheumatology Clinic of the University Hospital of Ioannina during the period 1991-2000. All patients fulfilled the American College of Rheumatology criteria for RA. The demographic, clinical, laboratory, radiological and therapeutic characteristics of the disease at diagnosis, and at the last follow-up were analyzed according to gender.

Results

We studied 312 women and 126 men with early RA. The female to male ratio was 2.5: 1 and the mean age at diagnosis was 49.4±14.9 years for women and 55.3±15.6 years for men ($P < 0.0003$). Women had a longer duration of follow-up ($P<0.0003$). There were no differences between genders in the general symptoms or the symmetricity of joint involvement at disease onset. However, at disease onset women had a higher erythrocyte sedimentation rate (ESR) (>30 mm/1st hour), although there were no significant differences between the two groups concerning the rest of the clinical, laboratory and radiological findings. At the last follow-up women still had a higher ESR (>30 mm/1st hour), but no significant differences were found between the two groups concerning the rest of the parameters investigated independently of the follow-up duration. Finally, women and men showed the same degree of radiological changes and functional ability and were treated similarly except for the more frequent use of hydroxychloroquine in women.

Conclusion

It seems that gender does not significantly influence the expression of RA.

Key words

Early rheumatoid arthritis, sex, women, men, early treatment.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology with a variable course and outcome among patients. Disease manifestations are caused by a chronic, destructive, inflammatory response that primarily affects the synovial membrane but can also target extraarticular tissues, resulting in organ failure (1). Improvement of the current treatment of RApatients will require the identification of factors that modulate the expression, aggressiveness and progression of the disease (2, 3).

Previous studies have shown that disease severity and outcome could be influenced by a variety of factors such as gender (4), race (5, 6), age at disease onset, duration of disease (7-9), joint score for pain and swelling, systemic manifestations and radiological changes (10-14). Furthermore, the values of the acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) (15-18), the presence of rheumatoid factor (RF) (18-23) and the HLA phenotype (24-28) may also influence the disease expression and outcome.

RAis more frequent in women (female to male ratio: 2 or 3 to 1) (29) although extraarticular manifestations such as rheumatoid vasculitis affect equal proportions of both sexes (30,31). Furthermore, there is heterogeneity between men and women in the effect of the HLA-DRB1 shared epitope on the susceptibility and clinical expression of RA (32, 33). In addition, there have been few studies concerning the influence of age on the course of early RA (34). The above observations raise the possibility that gender modifies disease expression, possibly in conjunction with HLA genes. The purpose of the present study was to investigate the possible association of gender with disease expression in a group of 454 Greek RApatients.

Materials and methods

The clinical and laboratory characteristics of 454 patients with early RA (disease duration prior to diagnosis less than 1 year and age greater than 16 years) were studied. The 454 participants were all patients with early RA who were registered at the Department of Rheumatology of the University Hospital of Ioannina, Greece during the period 1991 - 2000.

All patients fulfilled the American College of Rheumatology (ACR) criteria for RA(35). All were examined during the follow-up at pre-defined times according to a standardized protocol. At each visit, every patient had a complete physical examination and routine laboratory tests including ESR. The data of the patients were extracted from medical records, retrospectively based on standardized files, by two of the authors (PVV and IAP). Data concerning the demographic, clinical, laboratory and radiological parameters as well as the treatment were recorded in a computer database at two time points: the time of diagnosis and at the last follow-up. Exclusion criteria included symptoms, signs or a family history of psoriasis, inflammatory bowel disease, ankylosing spondylitis, Reiter's syndrome, polymyalgia rheumatica or juvenile RAas well as prior use of disease modifying antirheumatic drugs (DMARDs) or steroids.

The following parameters were recorded for each patient: gender, age at diagnosis, duration of follow-up, distribution of joint involvement (mono- oligo- or polyarticular, symmetrical or asymmetrical involvement, small or large joints), morning stiffness (in minutes), grip strength (mmHg using a sphygmomanometer), and joint counts for pain and swelling, as well as the number of joints with deformities or ankyloses at the end of the follow-up.

All patients had wrist, hand and foot radiographs taken at the time of diagnosis and at the last follow-up; these were reviewed by the same investigator and scored according to Steinbrocker's grading system (grade I-IV) (36).

Laboratory parameters such as the CRP (normal values <6 mg/l), ESR (Westergreen, normal values <20 mm/1st hr), and RF (IgM RF - Latex test, normal values <80) were recorded.

The functional ability of the patients was measured at the last follow-up according to the American College of Rheumatology (ACR) functional abili-

ty grading system (stages I-IV) (37). A global evaluation of the disease was also made by both the patient and the physician on a 4-point scale: bad, medium, good or very good. Finally the different DMARDs used and the length of their administration during follow-up were studied.

Student's t-test and the χ^2 test were applied as indicated for the statistical analysis. In addition, multiple logistic regression analysis was carried out using gender as a dependent factor.

Results

From a total of 1,271 patients with RA, 454 patients were diagnosed with early RA. Nine patients were excluded because they had used various DMARDs and steroids prior to the study period. For 7 patients there were no medical records for various reasons. More specifically, 3 refused the treatment, 2 were lost to follow-up immediately after the diagnosis, one moved to another city, and one died from acute myocardial infarction before completing the first medical examination. Thus, 438 patients (312 women and 126 men) were included in the study.

Table I shows the main clinical characteristics of the patients, by gender. The female to male ratio was 2.5: 1. The mean age at diagnosis was significantly higher for men than for women. Women were also found to have a significantly longer duration of follow-up in the outpatient clinic.

There were no significant differences between the two genders in the general symptoms (fever, weight loss) or in the symmetricity of joint involvement at disease onset. There were no differences between the two groups concerning the type of joints involved (small – large joints, upper – lower limbs) at disease onset, although there was a higher frequency of small to medium joint involvement of the upper limbs (this difference was not statistically significant).

Based on the results of multivariate analysis, gender appeared to be an independent factor associated with ESR (> 30 mm/1st hour) at disease onset (Table II). Gender was also significantly associated with ESR (> 30 mm/1st hour) at the last follow-up (Table III).

Regarding the level of functional ability between groups, no significant differences were found and the total percentage of patients with functional ability in categories III and IV was less than 10% of the total number of patients for each of the two groups. More than two-thirds of the patients were found to have a good or very good level in the global evaluation by the patient and doctor (Table IV). Furthermore, the drug treatment was similar for the two groups, with only an increased usage of hydroxychloroquine in the female group (Table V).

Table I. Demographic characteristics of early rheumatoid arthritis patients at the time of diagnosis.

	Women (n = 312)	Men (n = 126)	P
Age at diagnosis (years) (mean ± SD [range])	49.4 ± 14.9 (16-84)	55.3 ± 15.6 (17-83)	0.0003
Disease duration before diagnosis (years)	0.6± 0.4	0.3± 0.2	NS*
Follow-up (years)	5 ± 4.1	3.8± 3.5	0.0003
Fever no. (%)	70 (22.4)	23 (18.3)	NS
Weight loss no. (%)	19 (6.1)	10 (7.9)	NS
Type of onset no. (%)			
monoarthritis	4 (1.3)	3 (2.4)	NS
oligoarthritis	32 (10.3)	16 (12.7)	NS
polyarthritis	276 (88.5)	107 (84.9)	NS
Symmetrical onset no. (%)	297 (95.2)	117 (92.8)	NS

*Not significant

Table II. Logistic regression analysis for clinical, laboratory and radiological characteristics at first assessment. Dependent factor: gender (women/men). Adjusted for age.

Parameters	Odds ratio	(95% CI)	P
Morning stiffness (> 10 min)	1.02	(0.55 - 1.89)	NS*
Number of tender joints (> 6)	0.91	(0.42 - 1.95)	NS
Number of swollen joints (> 6)	1.36	(0.69 - 2.69)	NS
C-reactive protein (> 10 mg/l)	0.69	(0.40 - 1.17)	NS
Erythrocyte sedimentation rate (> 30 mmHg)	2.21	(1.27 - 3.83)	< 0.01
Rheumatoid factor positivity	1.13	(0.70 - 1.83)	NS
Radiographic score (Steinbrocker III, IV)	1.27	(0.63 - 2.58)	NS

*Not significant

Table III. Logistic regression analysis for clinical, laboratory and radiological characteristics at the last follow - up. Dependent factor: gender (women/men). Adjusted for age and follow - up duration.

Parameters	Odds ratio	(95% CI)	P
Morning stiffness (>10 min)	1.53	(0.73 - 3.19)	NS*
Number of tender joints (>6)	2.31	(0.71 - 7.56)	0.08
Number of swollen joints (>6)	0.50	(0.15 - 1.69)	NS
C-reactive protein (>10 mg/l)	0.69	(0.37 - 1.26)	NS
Erythrocyte sedimentation rate (>30 mmHg)	2.82	(1.49 - 5.36)	< 0.01
Rheumatoid factor positivity	0.95	(0.55 - 1.64)	NS
Radiographic score (Steinbrocker III, IV)	1.29	(0.64 - 2.79)	NS

*Not significant

Table IV. Functional ability and global assessment of men and women with early rheumatoid arthritis.

	Women (n = 312) n (%)	Men (n = 126) n (%)	P
ACR* functional class			
stage I	97 (63.1)	87 (69.0)	NS**
stage II	86 (27.5)	30 (23.8)	NS
stage III	23 (7.4)	5 (4.0)	NS
stage IV	6 (1.9)	4 (3.2)	NS
Physician assessment***	228 (73.1)	99 (78.6)	NS
Patient assessment***	206 (66.0)	91 (72.2)	NS

*American College of Rheumatology; **not significant; ***percent rated as good or very good.

Table V. The number of patients treated with different disease modifying anti-rheumatic drugs in early rheumatoid arthritis.

Disease modifying anti-rheumatic drugs (DMARDs)	Women (n = 312) n	%	Men (n = 126) n	%	P
Hydroxychloroquine	136	43.6	32	25.4	0.05
Gold injections	40	12.8	18	14.3	NS*
Penicillamine	119	38.1	45	35.7	NS
Methotrexate	174	55.8	59	46.8	NS
Cyclosporine A	56	17.9	15	11.9	NS
Azathioprine	9	2.9	3	2.4	NS
Oral steroids	159	51.0	61	48.4	NS
DMARD discontinuation					
due to inefficacy	47	15.1	15	11.9	
due to adverse events	39	12.5	18	14.5	
Number of different DMARD/patient per year of follow-up		0.4±0.2		0.5±0.3	NS

*Not significant.

Discussion

RA is a multi-factorial autoimmune disease. The interplay of genetic, environmental and hormonal factors plays a pivotal role in its pathogenesis. The identification of variables that modulate the expression and progression of RA will help to improve current management.

Previous studies suggest that RA in Mediterranean countries is a milder disease compared to northern European countries (38, 39). Dietary (Mediterranean diet) (40,41), environmental (mild climate, sunlight) and genetic factors (42,43) may contribute to this milder form of the disease which is expressed clinically by less joint and systemic involvement, as well as radiographically with less severe joint damage. In addition, a lower incidence and prevalence of RA were found (44) and a lower frequency of the HLA-DRB1 motif was present (43). Recent studies from our group showed that RF positive early RA patients had a worse outcome compared to seronegative patients (45) and the age at disease onset did not influence the clinical course or outcome of early RApatients (46).

In the present study we investigated whether gender is an independent parameter that modifies disease expression in early RA patients. Gender-related differences in susceptibility as well as in disease phenotype may result in the male and female variants of RA. To test this hypothesis, since the above distinctions are important for pathophysiologic considerations as well as therapeutic decisions, we compared the pattern of disease involvement in female and male patients with early RA.

The disease diagnosis was made by specialist rheumatologists in order to maintain strict diagnostic criteria and a detailed recording of clinical and laboratory parameters. In addition, treatment was commenced at a very early stage of the disease using various DMARDs.

Our study confirmed that women are affected more frequently (female to male ratio 2.5: 1) and at a younger age in comparison to men. The latter is in contrast with previous studies (46). In addition, women had a longer length of follow-up. Nevertheless, apart from a higher ESR (>30 mm/1st hour), there were no significant differences in the rest of clinical and laboratory parameters between the two groups at disease onset. At the last follow-up only ESR (> 30 mm/1st hour) was found to be higher in women independent of the duration of follow-up. Previous studies have shown conflicting results concerning the influence of gender on the disease course. Some investigators have reported that women had a worse course, outcome and survival rate (7, 19, 48), while others found no significant differences between the genders. Finally, some studies showed a worse prognosis and mortality in men (8, 49, 50).

Long disease duration, polyarthritis in combination with higher CRP values and ESR have been related to erosive changes on joint radiographs and a reduced functional ability in patients (15,51). Although women had higher ESR (>30 mm/1st hour) values compared to men, there were no significant differences in the functional ability of the two groups, with less than 10% of the patients being classified in categories III and IV. However, Weyand *et al.* found that men had erosive disease more frequently and it tended to occur earlier, while joint surgery for structural consequences were performed mainly in women (4). In contrast Saraux *et al.* studied a large number of patients and found that joint destruction was associated with female gender. Another study from the same group showed that men had a lower risk of severe joint destruction than women (52).

RF is associated with more severe disease (27). However, it is impressive

that no significant difference in RF positivity was found in the above studies, including ours, although conflicting results concerning erosive disease have been reported. Extraarticular manifestations are rare in Greek patients (38). Weyand *et al.* found nodules and lung involvement more frequently in men, while women developed sicca syndrome more frequently (4). However, Alarcon proposed that lung involvement may be attributable to higher rates of smoking and an increased likelihood of exposure to other environmental toxins in men by virtue of their lifestyle or occupation (53). Nevertheless, other studies showed a higher risk of serositis and vasculitis in men (44, 54-56).

Some investigators have suggested a correlation between gender and the commencement of second-line management, with women showing a delay from onset of symptoms to DMARDs treatment (57). Our study showed no differences in the use of DMARDs except for the greater amount of hydroxychloroquine used in women. This may reflect the fact that a milder drug was used prior to other DMARD treatment in women.

The present study found that gender does not seem to affect the expression of early RA, confirming previous reports (58). However, there are some limitations in the interpretation of our data which are: i) its retrospective character, ii) the evaluation of radiographs using the Steinbrocker score, which gives qualitative information rather than the Larsen or Sharp scores which give a more quantitative score damage, and iii) the follow-up period was variable among the patients, and there was no data on the reasons for follow-up cessation. Women were found to have a longer disease duration. This could be related to: i) the longer follow-up due to better compliance that women exhibited, and ii) the increased mortality among men due to factors not always related to the onset of RA. As a consequence, the possibilities for comparing the course and outcome of the disease based on the follow-up are limited. On the other hand, our study comprised: i) a relatively large number of patients, ii) the use of strict entry criteria, excluding patients with psoriatic arthritis or polymyalgia rheumatica, iii) the identification of early RA patients without prior use of DMARDs or steroids, and iv) early immunointervention before the development of bone deformities or joint ankyloses.

In conclusion, the present study indicates that gender does not significantly influence the clinical expression of early RA. Early diagnosis and a similarly early treatment strategy for both women and men seem to result in a more favorable disease outcome.

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