Influence of Sex on Disease Severity in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether patient's sex influences the severity of rheumatoid arthritis (RA) in terms of clinical severity or need for treatments.

Methods. This was a retrospective, single-center study. We compared 133 male patients with 133 female patients presenting with RA and matched for disease duration. Data collection included demographic characteristics, pattern of joint involvement, extraarticular manifestations, medical treatment, and joint surgery. Biological measures, HLA genotypes, Larsen radiological scores on radiographs of hands and feet, and Health Assessment Questionnaire (HAQ) results were obtained.

Results. Mean disease duration was 7.4 ± 6.9 years. Concerning clinical pattern of involvement, sicca syndrome was more frequent in women than in men ($p = 0.0003$). There were no significant differences concerning absence or presence of at least one disease associated gene (HLA-DRB1*01 or *04) in our patients; however, women more often carried 2 disease associated genes (21% vs 11%). No other difference in clinical, biological, or radiological indicators was noted between the 2 populations. Concerning treatment, there was no difference for large joint arthroplasties; female patients underwent significantly more distal joint arthrodesis, 6.7% vs 1.5% ($p = 0.03$); they were prescribed slightly more disease modifying drugs, 3.33 vs 2.83 ($p = 0.04$); and showed a trend toward more large joint arthrodesis, 15% vs 7.5% ($p = 0.05$), and metacarpophalangeal joint arthroplasties, 5.2% vs 0.7% ($p = 0.08$).

Conclusion. When patients are matched for RA duration, sex has little effect on the disease pattern and severity, yet women undergo more distal joint surgery. (J Rheumatol 2005;32:1448–51)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SEX HLA GENES SURGERY

Rheumatoid arthritis (RA) is currently recognized as a heterogeneous entity that is usually diagnosed with reference to the American College of Rheumatology (ACR) classification criteria[1]. The clinical course of RA is variable and its outcome is difficult to predict. In many patients, the disease process is severe and results in progressive joint destruction and severe disability, but outcomes vary widely. RA is recognized as a genetically complex disease. The complexity relates to the incomplete penetrance and multiple predisposing genes in disease pathogenesis. As in other common genetic diseases, multiple genes are responsible for its predisposition or protection. Allelic polymorphisms within the HLA-DRB region play an important role in RA[2]. Disease associated HLA-DRB1* alleles impart susceptibility but also contribute to the progression of the disease, influencing disease severity and pattern[3]. Studies involving HLA-DRB1* alleles have also shown unevenness in the sex distribution in different clinical categories of RA: while women outnumbered men by a factor of 2 among patients with mild to moderate disease, which is consistent with previous incidence studies, rheumatoid vasculitis affected both sexes equally[4]. This observation raises the possibility that sex modifies disease expression. A sexual dimorphism of RA could result from sex related differences in penetrance as well as in disease phenotype. It has long been known that the prevalence of RA is increased in women. However, it is unclear whether female sex simply increases the penetrance of the disease or whether sex-specific mechanisms modulate the disease process in a more complex manner. In this case-control study we investigated whether the profile of clinical and biological manifestations is similar in male and female patients with RA matched for disease duration.

MATERIALS AND METHODS

Patients. All male outpatients who fulfilled the ACR criteria for RA[1] and who received medical care at a single tertiary referral hospital unit between 1996 and 1998 were enrolled. This hospital is the main referral center for

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rheumatic diseases in the county. For each case patient, one female control patient matched for RA duration was selected. Control cases were restricted to RA diagnosis according to the ACR criteria and followup at our center in the same time interval. They were selected from a cohort of 265 women followed in another study[5], recruited between 1995 and 1997, and were selected by RA duration (closest RA duration to that of a male case patient). An absolute maximal difference of 6 months in RA duration was allowed between a case patient and a matched control. After selecting women controls by disease duration, we randomly selected one control per case through a computer generated allocation.

Data collection. All patients were informed that their data would be analyzed; information was given and consent was sought orally. The entire medical record of each patient was reviewed to obtain the followup data, according to a standardized information sheet. The following evaluation data were collected: age, sex, disease duration (defined from time of diagnosis), presence and type of extraarticular manifestations (sicca syndrome, nodules, Raynaud syndrome, pericarditis, vasculitis), and medical treatment [disease modifying drugs (DMARD) and corticosteroids]. Diagnosis of sicca syndrome was based on objective ophthalmologic findings and/or the patient's use of artificial tears. Recourse to surgical interventions was noted and divided into 5 groups: synovectomies, large joint arthroplasties (shoulder, elbow, hip, knee), large joint arthrodeses (tibiotarsal, rear foot, medial foot, wrist, cervical spine), distal joint arthrodeses (fingers, toes), and metacarpophalangeal (MCP) arthroplasties (Swanson arthroplasties). At the time of study, we performed a cross-sectional clinical and biological evaluation and evaluated IgM rheumatoid factor (RF) status by nephelometry and antinuclear antibody (ANA) status by immunofluorescence on HEp-2 cells. HLA-DRB1* and DQB1* genotyping was performed by oligonucleotide typing after polymerase chain reaction amplification. We considered that HLA-DRB1*01, *0401, *0404, *0405, and *0408 alleles represented the disease associated genes. From available patients we also obtained Health Assessment Questionnaire (HAQ) scores and hand, wrist, and foot radiographs, which were scored according to Larsen method[6]: for each patient, a total damage score was noted for the hands and feet.

Statistical analysis. Statistical analysis was performed using BMDP statistical software. Bivariate analysis of qualitative data was performed using a paired chi-square test, with Yates' correction when appropriate, or Fisher's exact test if appropriate. For quantitative data, a variance analysis was used for normal distributions and the nonparametric Kruskal-Wallis test for other distributions. When these variables were continuous, they were transformed into categorical variables using the median value as the cutoff point. The significance level was set at 0.05.

RESULTS

Demographic and clinical features of the patient cohort. A total of 137 male patients were enrolled in this study; final analysis concerned 133 male and 133 female patients with complete data collection and disease duration matching (for 4 male patients, no disease duration matching was available). Characteristics of the patients are given in Table 1. Mean disease duration was 7.4 ± 6.9 years for the whole sample. The mean age at disease onset was 51.4 ± 13.2 years for men and 48.7 ± 14.8 years for women (no significant difference).

Sicca syndrome was more frequent in women: 35% versus 16% ($p = 0.0003$). No other extraarticular involvement difference was noted. HAQ scores were also comparable.

Biological features and radiological scores of the patient cohort are given in Table 1. The percentage of patients positive for RF or ANA at one point during followup was similar in the 2 groups, as was the total Larsen score.

HLA-DRB1* genotype results are shown in Table 2. There were no differences in HLA-DRB1*04 or *01 distributions between men and women. It was found that 72.0% of men and 70.7% of women presented at least one disease associated gene, and the difference was not significant; however, there were more women with 2 disease associated genes (21% vs 11% men; $p = 0.03$).

Medical and surgical treatments. Analysis of the number of DMARD prescribed over the duration of followup showed significantly more DMARD for women (Table 3): mean number of DMARD was 3.3 ± 2.3 for women compared to 2.8 ± 1.8 for men ($p = 0.04$); 43.6% of women versus 32.3% of men ($p = 0.05$) received more than 3 DMARD over the duration of followup. There was no difference in use of corticosteroids.

Concerning surgery, there was no difference for recourse to synovectomies or large joint arthroplasties. Women underwent more distal joint arthrodeses (6.7% vs 1.5%; $p = 0.03$) and showed a trend toward more large joint arthrodeses (15% vs 7.5%; $p = 0.05$) and MCP joint arthroplasties (5.2% vs 0.7%; $p = 0.08$) (Table 3).

DISCUSSION

Overall, in this retrospective study on 133 male and 133 female patients with RA matched for disease duration, we found that sex had little effect on the disease pattern and severity. After a median followup of 7 years, we observed no differences in outcome between women and men, radiographically, by a functional score (HAQ), or by large joint surgery. However, women underwent more distal joint arthroplasties and showed a trend toward more large joint arthrodeses and more MCP joint arthroplasties, as well as DMARD use. This result is interesting, and surprising in the light of the radiographic results, which showed no difference in severity between the 2 groups. Few investigators have specifically studied recourse to surgery according to sex. Weyand, *et al*[7] retrospectively compared 55 male and 110 female patients with RA matched for disease duration: they also found more recourse to surgery for women although radiographic results were comparable. This suggests that rheumatoid joint destruction is perhaps more disabling in female patients, thus leading to more surgery. Concerning DMARD use, one other report[8] describes an association with sex in a retrospective analysis of 135 male versus 174 female RA patients; however, the association was reversed, men being prescribed more DMARD (2.7 vs 2.3 over 16 years of followup). Our results concerning DMARD should probably be interpreted with caution, since the type and "aggressiveness" of the DMARD was not noted.

In our study the pattern of extraarticular involvement differed only for keratoconjunctivitis sicca; this is concordant with the results from Weyand, *et al*[7]; however, they also observed more nodules and lung and pericardial disease in

Table 1. Clinical, biological, and radiological characteristics of male and female RA patients matched for disease duration.

Characteristic	Male Patients, n = 133	Female Patients, n = 133	p
Age at onset, years, mean ± SD	51.4 ± 13.2	48.7 ± 14.8	0.12
Extraarticular manifestations (%)			
Sicca syndrome	21/131 (16.0)	46/130 (35.4)	0.0003
Nodules	30/133 (22.5)	25/133 (18.7)	0.44
Raynaud syndrome	16/131 (12.2)	22/130 (17.0)	0.28
Pericarditis	7/133 (5.2)	6/133 (4.5)	0.77
Vasculitis	4/133 (3.0)	2/133 (1.5)	0.40
HAQ score, mean ± SD	1.08 ± 0.84	1.18 ± 0.65	0.26
Rheumatoid factor positivity	88/130 (67.7)	82/133 (61.7)	0.30
Antinuclear antibody positivity	21/124 (16.9)	29/130 (22.3)	0.28
Total Larsen score, mean ± SD	50.6 ± 44.5	54.4 ± 50.9	0.80

Unless otherwise indicated, results are number of patients, numerator is number of patients for whom data was available. Cutoffs for rheumatoid factor and antinuclear antibody positivity: ≥ 20 IU/ml and ≥ 1/100, respectively. HAQ: Health Assessment Questionnaire.

Table 2. HLA-DRB1 genotyping of male and female RA patients matched for disease duration.

Alleles	Male Patients, %	Female Patients, %	p
DRB1*04†	51/118 (44.1)	71/133 (53.4)	0.14
DRB1*01	36/118 (30.5)	36/133 (27.1)	0.54
DRB1*01/01 or 01/04† or 04/04†	13/118 (11.0)	28/133 (21.1)	0.03
DRB1*01 and/or *04†	85/118 (72.0)	94/133 (70.7)	0.81

Results are number of patients, numerator is number of patients for whom data was available. † DRB1*04 = 0401, 0404, 0405, or 0408 alleles.

Table 3. Treatment of male and female RA patients matched for disease duration: use of corticosteroids, DMARD, and surgery.

	Male Patients, n = 133 (%)	Female Patients, n = 133 (%)	p
Corticosteroid treatment	79 (59.4)	85 (63.9)	0.46
No. of DMARD, mean ± SD	2.8 ± 1.8	3.3 ± 2.3	0.04
More than 3 DMARD†	43 (32.3)	58 (43.6)	0.05
Synovectomies	24 (18.0)	19 (14.2)	0.40
Large joint arthroplasties	16 (12.0)	16 (12.0)	1
Large joint arthrodesis	10 (7.5)	20 (15.0)	0.05
Distal joint arthrodesis	2 (1.5)	9 (6.7)	0.03
MCP arthroplasties	1 (0.7)	7 (5.2)	0.08

SD: standard deviation, MCP: metacarpophalangeal. † Median number of DMARD = 3.

men. In our study, lung disease was not investigated. It appears that either the salivary gland is a preferred target of rheumatoid disease in women, or women have more secondary Sjögren's syndrome, which might be viewed as a comorbidity, rather than a manifestation of rheumatoid disease. There were no significant differences in HLA-DRB1 distributions concerning HLA-DRB1*01 or *04 or presence of at least one disease associated gene; however, more women carried 2 disease associated genes. Other studies have found the opposite: expression of 2 disease associated molecules in higher frequency in men[3,8]. However, these studies were of small cohorts; as well, our results might be influenced by our recruitment characteristics (tertiary care) and perhaps by left censorship. Clearly, the difference in distribution of RA associated genes between men and women should be studied more fully, through larger cohorts.

The mechanisms by which sex related factors influence RA penetrance and clinical pattern are not understood. The greater prevalence among women suggests a hormonal basis for the development of RA. In male patients with RA, lower testosterone concentrations and higher follicle-stimulating hormone and luteinizing hormone concentrations have been

found[9], and it is not known whether such differences are a cause or a consequence of RA. Whether these hormonal effects interact with HLA-DRB1 genotypes has yet to be investigated, but could potentially account for the possible different genotypic pattern of RA penetrance in men and women. Other explanations for sex related difference in RA could be related to lifestyle, comorbidities, or genetics. A recent study of a murine model of RA concluded that disease susceptibility and onset showed predominant linkage with the female sex, under the control of a locus on the X chromosome, while the severity loci were more strongly linked to the male sex[10]. It should also be noted that some important variables were not addressed, such as cigarette smoking.

Data concerning the prognostic value of sex in RA are conflicting. Indeed, van der Heijde, *et al*[11] in 1988 reviewed 13 studies in which prognostication on the basis of sex was considered. Eight studies indicated that male sex was associated with a better prognosis, 4 stated there was no effect of sex, and one correlated male sex with a worse outcome. Several more recent predictive studies have not found sex to be predictive of poor prognosis[12-14]. It appears that sex drops out when more strongly predictive factors (e.g., damage at baseline or RF status) are entered.

We did not investigate mortality rates; however, Anderson reviewed the existing literature on the effect of sex and age on mortality in RA[15]. Ten articles were reviewed: the results failed to show a clear association between sex, age, and mortality. Recently it was suggested that excess cardiovascular mortality in RA is greater in women than in men[16].

Our study was retrospective and presents the usual limitations of a retrospective case-control design. However, in favor of the representativeness of the study group, it should be noted that our clinic is the main referral center for rheumatic diseases in the county, and all men followed in our center were included. Patients were carefully matched for disease duration and the number of patients studied is relatively consequential.

We found no evidence for a role of sex in predicting severity in RA; yet women had more recourse to distal joint surgery and more DMARD use, which suggests that in our center women are treated more aggressively, for an equivalent severity. This should be investigated further by prospective studies and confirmed in other centers.

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