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Determinants of disease course in rheumatoid arthritis

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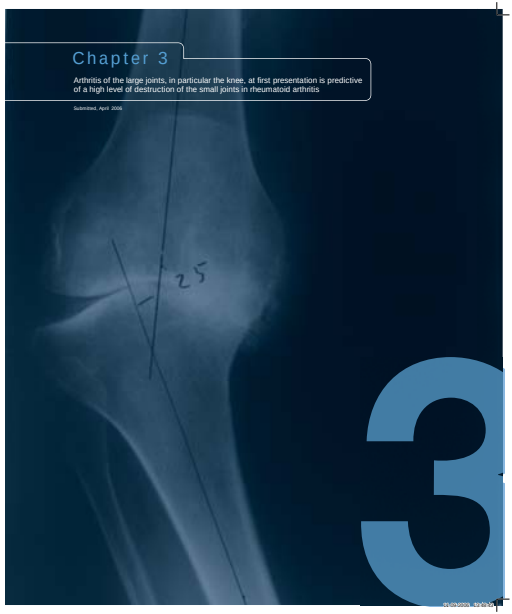

Chapter 3

Arthritis of the large joints, in particular the knee, at first presentation is predictive of a high level of destruction of the small joints in rheumatoid arthritis

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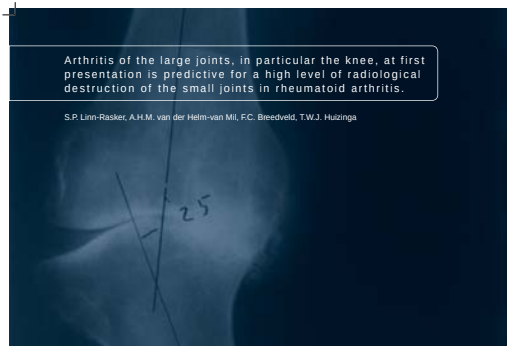

Arthritis of the large joints, in particular the knee, at first presentation is predictive for a high level of radiological destruction of the small joints in rheumatoid arthritis.

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Abstract

Objective **To investigate the predictive value of the distribution of inflamed joints at first presentation for the severity of the disease course in RA.**
Methods **From 1009 consecutive patients included in the Leiden Early Arthritis Clinic, 285 patients fulfilled the ACR-criteria for RA within 1-year of follow-up. Of these, 28 patients achieved remission. Radiographs of hands and feet were scored according to the Sharp-van der Heijde method and the 28 patients with the most destructive disease were selected. The distribution of inflamed joints of the patients with the extreme disease courses was compared. The association between the distribution of inflamed joints and the level of destruction of the joints of hands and feet in the whole group of RA-patients was assessed using regression analysis.**
Results **Comparison of the patients with extreme disease courses using univariate and logistic regression analyses revealed that arthritis of the large joints, in particular the knee, was associated with severe RA. In the whole group of RA-patients, the total number of swollen joints and the presence of knee arthritis associated independently with the level of destruction of the small joints. RA-patients with knee arthritis had higher C-reactive protein levels than patients without knee arthritis and investigating the distribution of inflamed joints together with other variables yielded the number of swollen joints, C-reactive protein level, presence of anti-CCP antibodies and symptom duration as predictors for RA severity.**
Conclusion **Arthritis of large joints, in particular the knee, at first presentation is associated with a destructive course of RA.**

Keywords **Rheumatoid arthritis, severity, prediction, distribution inflamed joints.**

Introduction

The initial clinical presentation of rheumatoid arthritis (RA) is variable and the number as well as the distribution of inflamed joints may vary between a monoarthritis and an extensive polyarthritis. In general, RA is considered to be a chronic potentially destructive disease, but the severity of the disease course for an individual patient is difficult to predict at baseline. RA patients who present with an extensive polyarthritis may have a mild disease course or remit spontaneously, while patients who initially present with a monoarthritis may experience a severe destructive course of the disease. The implication of being able to predict the disease course in RA is obvious, given the value of early treatment and the common use of aggressive treatment strategies[1-3]. Several studies have assessed associations between clinical variables and RA severity[4-17]; in these studies the presence of morning stiffness, symptom duration >6 months, rheumatoid factor (RF), antibodies against cyclic- citrullinated peptides (CCP), early radiological erosions and an elevated C -reactive protein (CRP) were correlated with a more severe outcome of the disease[4-17]. So far, it is not known whether the distribution of inflamed joints is associated with the disease outcome in RA. Therefore, the present study aimed to investigate the predictive value of the distribution of inflamed joints at first presentation for the severity of the disease course in RA. In order to identify the joints that are associated with a severe disease outcome, the distribution of swollen joints of RA-patients with extreme disease courses, sustained remission and progressive erosive disease, were compared. The comparison of the extremes of phenotypes may reduce the risk of missing risk factors caused by regression to the mean and this approach, in addition to studying the whole group of patients, may lead to detection of additional prognostic factors. Subsequently, in the whole group of RA-patients the association between the distribution of inflamed joints at baseline and the level of radiological destruction of the small joints of the hands and feet during follow-up was determined and the ability of the identified joints to predict RA severity in relation with other clinical parameters was assessed.

Patients and methods

Patients

For this study, patients from the Leiden Early Arthritis Clinic, a population-based inception cohort of patients with newly diagnosed early arthritis were selected. This cohort started in 1993 at the department of Rheumatology of the Leiden University Medical Center, the only referral center for rheumatology in a health care region of ~400,000 inhabitants in the Netherlands.
General practitioners were encouraged to refer patients directly when arthritis was suspected; patients were included if physical examination revealed arthritis (for further reading see[18]). In the study period (1993-1999), 1009 patients with early arthritis were included. After one year follow-up, 285 patients had fulfilled the 1987 ACR-criteria for RA[19]. From these RA patients, two categories of patients with extreme disease courses were selected: those who entered sustained remission (remitting RA) and those had progressed to the most destructive disease (severe RA). Remission was defined as satisfying the proposed American Rheumatism Association (ARA) criteria for clinical remission[19] after having discontinued the use of Disease Modifying Antirheumatic Drugs (DMARDs) for at least one year. After one additional year of follow-up the presence of sustained remission was confirmed. 28 patients had achieved sustained remission after mean disease duration of 3.7 years (range 210-3159 days SD 852 days). For more details on these patients see[20]. The remitting patients are further referred to as "remitting RA". Radiographs of the hands and feet were taken at baseline and yearly thereafter and the level of radiological joint destruction was scored according to the Sharp-van der Heijde method[21,22]. The rheumatologist that scored the radiographs was unaware of the study question. The patients with the most destructive disease course were identified by selecting the 28 patients that had the highest Sharp-van der Heijde scores after one year of follow-up. This corresponded with a Sharp-van der Heijde score >34 (mean 59). These patients are further referred to as "most severe RA".

Methods

At inclusion the rheumatologist questioned the patient about the initial symptoms as well as the presence of morning stiffness and the symptom duration.
Physical examination at baseline included a swollen joint count, scaling each joint on a 0-1 scale (0 denotes no swelling and 1 indicates the presence of swelling). Subsequently, the joints or joint groups were categorized (e.g. all metacarpophalangeal joints on one side were counted as one joint). The following joint(groups) were studied: shoulders, elbows, wrists, metacarpophalangeal joints, proximal and distal interphalangeal joints, knees, ankles and metatarsophalangeal joints. For the analysis a dichotomous approach was used that indicated the presence or absence of swelling per joint group.
Baseline laboratory parameters included ESR, CRP, IgM

rheumatoid factor ELISA as previously described[16] and anti-CCP2 antibodies (ELISA, Immunoscan RA Mark 2, Euro-Diagnostica, Arnhem, The Netherlands).
According to the instruction of the manufacturer a level > 25 arbitrary units was considered positive.

Statistical analysis

The baseline parameters of the patients with remitting and severe RA were compared using the Mann-Whitney test for continuous variables and the chi-square test for nominal variables. Subsequently, a logistic regression analysis with backward selection procedure (p>0.10 as removal criteria, using likelihood ratio test) was performed with the presence of remitting RA or most severe RA as dependent variable and the individual joint groups that were significantly associated with the disease outcome in the univariate analysis and the total number of swollen joints as possible explanatory variables.
To validate the findings, the association between the joint groups and radiological joint destruction was assessed in the total group of RA patients. The Sharp van der Heijde scores at 1 year follow-up were entered as a dependent variable in a linear regression analysis (backward selection procedure, p>0.10 as removal criteria) with the total number of swollen joints and the joint count for the individual joint groups as possible explanatory variables. To assess the association between the distribution of swollen joints and the level of radiological joint destruction in relation to other clinical variables that might be associated with RA severity, an other linear regression analysis (backward selection procedure, p>0.10 as removal criteria) was performed. In this analysis the Sharp van der Heijde score at one year follow-up was entered as a dependent variable and the total number of swollen joints, the swollen joint count for the individual joint groups, gender, age, the presence of anti-CCP antibodies, RF, morning stiffness, the CRP-level and symptom duration and as possible explanatory variables. The statistical package for the social sciences (SPSS) version 11.0 (SPSS, Chicago, IL) was used to analyse the data. A p-value ≤0.05 was considered significant.

Results

Univariate comparison of patient characteristics at first presentation of RA patients with extreme disease courses

The patients in the remitting and most severe RA group had no significant differences in the distribution of gender, age and morning stiffness. The patients with the most severe disease course more frequently harboured RF and anti-CCP antibodies, had higher levels of CRP and had higher Sharp-van der Heijde scores at inclusion compared to patients with remitting RA (Table 1).
The patients with the most severe disease course also had a significantly higher number of swollen joints at first presentation than the patients with remitting RA.
The distribution of swollen joints was different between the two groups: the patients with the most severe RA had significantly more often arthritis of the shoulders, elbows, proximal interphalangeal joints, knees and ankles (Table 2). There was no difference in the prevalence of swollen metacarpophalangeal and metatarsophalangeal joints between the two groups of RA-patients.

Regression analysis in the RA patients with extreme disease courses

To investigate which joint (groups) were independently associated with the disease outcome, a logistic regression analysis with backward selection procedure was performed with the presence of remitting RA or most severe RA as dependent variable and the individual joint groups that were significantly associated with the disease outcome in the univariate analysis (shoulder, elbow, proximal interphalangeal, knee, ankle) and the total number of swollen joints as possible explanatory variables. In this analysis only the presence of a swollen knee (odds ratio 7.0, P=0.004) was significantly associated with the disease outcome (Table 3).

Regression analysis in all 285 RA patients

To validate the findings, the association between the distribution of swollen joints and radiological joint destruction was assessed in the total group of RA patients. The Sharp van der Heijde score at 1 year follow-up was entered as a dependent variable in a linear regression analysis with a backward selection procedure and the total number of swollen joints and all evaluated joint groups as possible explanatory variables. This analysis revealed that in the total group of RA-patients the total number of swollen joints (p=0.004) and swelling of the knee (p=0.03) were independently associated with the level of radiological joint destruction of hands and feet (Table 4). A similar analysis was performed with the Sharp-van der Heijde scores at 2 and 3 year follow-up as dependent variable (X-rays were available of respectively 202 and 162 patients). In these analysis only swelling of the knee associated independently with the level of radiological joint destruction (B=7.2, SE=3 .9, P=0.05 for the 2-year time point and B=3.5, SE=4.7, P=0.005 for the 3-year time point). Figure 1 displays the level of radiological destruction of the small joints of the hands and feet during three years of follow-up of the RA-patients that at first presentation did have and did not have arthritis of the knee (Figure 1).

In conclusion, regression analyses in both groups of RA-patients and using the approach of the extremes of the disease courses yielded the total number of swollen joints and particularly the presence of arthritis of the knee as independently associated with the level of joint destruction of the small joints of hands and feet during follow-up.

Predictive ability of distribution of swollen joints in relation with other clinical characteristics for RA severity

Next, we investigated the predictive ability of the presence of arthritis of the knee and the total number of swollen joints in relation to other clinical variables that are observed or described to be associated with a severe disease outcome: CRP, RF, anti-CCP antibodies, morning stiffness and symptom duration[9,17]. (Table 1). A linear regression analysis with a backward selection procedure revealed that the total number of swollen joints (B=0.9, SE=0.4, P=0.03), the presence of anti-CCP antibodies (B=8.4, SE=2.4, P=0.001), the CRP-level (B=0.02, SE=0.007, P<0.01) and the symptom duration (B=0.2, SE=0.04, P<0.001) were independently associated with the level of joint destruction after 1 year follow-up.

> *Regression analyses in both groups of RA-patients and using the approach of the extremes of the disease courses yielded the total number of swollen joints and particularly the presence of arthritis of the knee as independently associated with the level of joint destruction of the small joints of hands and feet during follow-up.*

In this analysis the presence of arthritis of the knee was not an independent predictor for disease severity.
The fraction of explained variation of this model was 0.2. As after correction for clinical variables in a regression analysis the presence of arthritis of the knee was not independently associated with RA severity, in contrast to the CRP-level, the presence of anti-CCP antibodies and the symptom duration, we hypothesized that these variables might be distributed differently among the RA-patients with and without arthritis of the knee.

Arthritis of the knee was present in 106 (39%) patients at first presentation. The presence of anti-CCP antibodies and the symptom duration, but also the variables age, gender, RF and morning stiffness were not significantly different between the RA-patients with and without arthritis of the knee. However, there was a significant difference in the level of CRP; RA-patients with arthritis of the knee at first presentation had higher CRP-levels (mean 48 mg/l, SD 35 mg/l) compared to RA-patients without involvement of the knee (mean 22 mg/l, SD 24 mg/l, P<0.001).

Discussion

The present study aimed to investigate the predictive value of the distribution of inflamed joints at first presentation for the severity of the disease course in RA and demonstrated using two different approaches that the presence of arthritis of large joints, and arthritis of the knee in particular, is independently associated with the level of joint destruction. In regression analysis both arthritis of the knee and the total number of swollen joints at baseline were significantly associated with a severe disease outcome. Since all RA-patients fulfilled the ACR-criteria and per definition had involvement of the small joints and as the presence/absence of arthritis was evaluated as a dichotomous variable per joint group, in the present study a difference in the total number of swollen joints reflects a difference in the number of swollen large joint groups. From all joints the presence of arthritis of the knee at baseline was the strongest predictor for a higher level of radiological destruction of the small joints of the hands and feet.

After the identification of the knee and the total number of swollen joints as predictors for severe radiological destruction of small joints, we were interested whether these parameters were of additional value to established parameters for disease severity (anti-CCP antibodies, RF, C-reactive protein, morning stiffness, symptom duration). Therefore, a linear regression analysis was performed that included not only the distribution and number of swollen joints but also other clinical variables. This analysis revealed a significant association between the level of

radiological joint destruction and the total number of swollen joints, C-reactive protein, anti-CCP antibodies and symptom duration. The presence of knee arthritis was not significantly associated with RA severity in this analysis. A post hoc analysis demonstrated that patients with arthritis of the knee had higher levels of CRP compared to the patients without arthritis of the knee.

So apparently the CRP-level is a stronger predictor for the level of joint destruction than the presence of an inflamed knee. Interestingly, the presence of anti-CCP antibodies was not different between patients with and without knee arthritis. These data suggest that inflammation of large synovial joints, like the knee, induces a higher amount of pro-inflammatory cytokines (among others Il-6) that subsequently triggers an increased production of CRP by the liver. Holt et al previously showed that in patients with inflammatory arthritis the concentration of synovial Il-6 in knee joints was associated with the plasma level of Il-6 and also with plasma level of CRP[24]. Although having arthritis of the knee was also correlated with a high level of CRP in the present study and the CRP-level appeared to be a better predictor for disease severity compared to knee arthritis, in clinical practice a physician establishes the presence of arthritis of large joints as the knee directly during the first visit, whereas laboratory results are not immediately available. Furthermore, the presence of an elevated CRP-level can also be caused by non-rheumatologic factors such as a transient infection. Since the present study aimed to investigate the predictive value of the distribution of inflamed joints for the disease outcome in RA, the finding that the presence of arthritis of large joints and the knee in particular is associated with a more destructive disease might be of help in clinical practice.

Studies that investigate the natural disease course in RA are nowadays hampered by the fact that aggressive and effective disease modifying antirheumatic drugs including biologicals are used. The effective reduction of the disease activity diminishes the level of joint destruction. Despite the indisputable benefit for RA patients, the natural course of the disease is altered and the patients who are currently treated for RA are less suitable for studies that aim to identify variables that predict the disease outcome. The patients included in the present study were treated for RA between 1993 and 1999. During this era, therapy with DMARDs was started in a relatively late stage and medications of choice were among others antimalarials, of which is known that their ability to halt disease progression is limited. None of the included patients was treated with biologicals. The 28 patients who out of achieved sustained remission 16 patients had received no DMARD therapy, 6 were treated with antimalarials and the remaining 7 were prescribed methotrexate or sulphasalazine. The patients included in the present study are more suitable for a study assessing risk factors for RA severity, than patients who are nowadays included in our Early Arthritis Clinic.

In conclusion, early recognition of patients with RA with a potentially severe disease course is important since these patients in particular may benefit from the therapeutic options that are currently available. It is already known that the presence of anti-CCP antibodies, symptom duration and CRP are associated with RA severity. This study reveals that also the presence of arthritis of large joints and particularly arthritis of the knee are predictive for a destructive disease course.

Table 1

Baseline patient characteristics of the RA patients with extreme disease courses

	Remitting RA N=28	Most severe RA N=28	P
Female, n (%)	18 (64)	17 (61)	0.7
Age, years, median (IQR)	59 (48-71)	59 (50-72)	1.0
Morning stiffness, minutes, median (IQR)	127 (30-180)	127 (30-180)	1.0
Symptom duration, days median (IQR)	127 (57-207)	152 (87-281)	0.1
C-reactive protein mg/l, median (IQR)	29 (7-46)	56 (26-75)	0.01
IgM RF positive, n (%)	6 (21)	23 (82)	<0.05
Anti-CCP 2 positive, n (%)	3 (11)	21 (75)	<0.05
Total number of swollen joints, median (IQR)	5.3 (3-7)	7.3 (5-9)	<0.05
Sharp-van der Heijde score, median (IQR)	0 (0-2)	10 (1-17)	<0.05

Table 2

Distribution of swollen joints of the RA patients with extreme disease courses

Joint group n (%)*	Remitting RA N=28	Most severe RA N=28	Odds ratio	95% CI	P
Shoulder	1 (3%)	6 (21%)	6.4	2.0-26.4	<0.05
Elbow	4 (14%)	8 (29%)	2.5	1.2-5.5	<0.05
Wrist	19 (68%)	21 (75%)	1.4	0.7-2.8	0.3
Metacarpophalangeal	23 (82%)	23 (82%)	1.0	0.5-2.2	1.0
Proximal interphalangeal	17 (61%)	23 (82%)	2.9	1.5-5.9	<0.05
Distal interphalangeal	1 (4%)	1 (4%)	1.0	0.2-4.1	1.0
Knee	7 (25%)	17 (61%)	4.7	2.5-9.0	<0.05
Ankle	4 (14%)	9 (32%)	2.9	1.4-6.3	<0.05
Metatarsophalangeal	8 (29%)	9 (32%)	1.2	0.6-2.7	0.6

* The numbers (percentages) indicate the number (percentage) of patients with swelling of (at least one of) the joints of the specific joint groups.

Table 3

Results of logistic regression analysis with backward selection procedure and remitting or severe RA as dependent variable and the total number of swollen joints and the joints with a significant result in univariate analysis as possible explanatory variables

Joint group	P	Odds ratio	95% CI
Shoulder	0.07	8.7	0.8-90.1
Elbow	0.08	4.1	0.9-19.4
Knee	0.004	7.0	1.9-25.9

Table 4

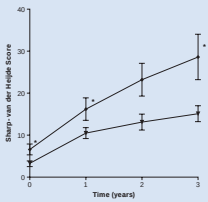
Results of linear regression analysis with backward selection procedure in the 28S RA-patients with Sharp-van der Heijde score at 1-year follow-up as dependent variable and distribution and total number of swollen joints as possible explanatory variables

Joint group	B*	SE	P
Knee	1.4	0.5	0.004
Total number of swollen joints	**6.1**	**2.9**	**0.03**

* Indicates regression coefficient

Figure 1

The level of radiological destruction of the small joints of hands and feet during three years of follow-up of RA-patients with and without arthritis of the knee at first presentation.



Legend to Figure 1

* P<0.05 (Mann-Whitney test). At the 2 and 3 year time point radiographs of hands and feet were available of 202 and 162 patients respectively

— no knee arthritis

— with knee arthritis at first presentation

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