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Does the season at symptom onset influence the severity of radiographic joint destruction in Rheumatoid Arthritis?

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ABSTRACT

Objective
Several season-associated environmental factors have been related to the onset of rheumatoid arthritis (RA) and the severity of joint complaints. However, whether seasonality affects the long-term outcome of RA is unknown. We aimed to evaluate the influence of the season at symptom onset on long-term radiographic progression in two large cohorts.

Methods
688 RA-patients included in the Dutch Leiden Early-Arthritis-Clinic (EAC) and 830 RA-patients included in the Swedish BARFOT-study were studied. Repeated radiological measurements during 7 and 5 years of follow-up, respectively, were scored according to the Sharp-van-der-Heijde method. The majority of patients were recruited in an era when early aggressive treatment was not yet the standard. Seasons were defined meteorologically.

Results
In both cohorts, the proportion of RA-patients who had their symptom onset in winter was larger than those for other seasons; though significance was noted only in the Swedish cohort (p=0.005). The radiological progression rates over time, in contrast, were not different in the four seasonal groups, neither in the Dutch (p=0.29) nor in the Swedish cohort (p=0.46).

Conclusion
Meteorologically defined seasons at symptom onset were not associated with the severity of joint damage in RA, making it unlikely that season-related environmental factors influence long-term outcome.
INTRODUCTION

The severity of the joint destruction in Rheumatoid Arthritis (RA) is highly variable between patients. Genetic factors explain only part of the variance in joint destruction\(^1\), hence environmental factors likely play a role as well. Several environmental factors such as infections or Vitamin D levels portray seasonal clustering, and seasonal factors are thought to influence RA\(^2-4\). Some studies observed that RA starts more frequently in winter than in other seasons\(^5,6\) and that both the onset and severity of symptoms are season-related.\(^7,8\) A seasonal effect for the onset of RA was not observed by others.\(^9\)

It has not been established whether the season of onset of first arthritis symptoms is related to the severity of joint destruction over time. A recent French study found that early arthritis patients whose symptoms started between January 1\(^{st}\) and June 30\(^{th}\) had more often erosive disease after one year than patients whose symptoms started in the second half of the year.\(^10\) However, long term effects of the season of symptom onset on progression of radiographic joint damage are unknown.

A finding of seasonal influences on the severity of RA would indicate that season-related pathogenic factors play a role in joint destruction. Therefore, we studied the possible effects of the season of onset of first symptoms on long-term progression of joint destruction in early RA-patients from two observational cohorts.

MATERIALS AND METHODS

Patients

In both cohorts RA was defined according the 1987-ACR criteria, written informed consent was obtained from all patients and approval by the local medical ethical committees was obtained.

Cohort 1 consists of 688 Dutch RA-patients included between 1993 and 2006 in the Leiden Early Arthritis Clinic, a population-based inception cohort.\(^1\) In all patients the self-reported date of symptom-onset was recorded. Hands and feet X-rays taken at baseline and yearly intervals till 7 years of follow-up were studied (total number of X-rays 4030, mean follow-up duration 4.9 years). All X-rays were chronologically scored by one experienced reader who was unaware of clinical data using the Sharp-van der Heijde score (SHS).\(^11\) The within reader ICC was 0.91.\(^1\) The treatment of these patients could be divided into three treatment periods. Patients included in 1993-1995 were initially treated with NSAIDs, patients included in 1996-1998 were initially treated with chloroquine or salazopyrine and patients included after 1999 were promptly treated with methotrexate or salazopyrine.
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Cohort 2 contains 830 RA-patients from the BARFOT project, a Swedish multicentre observational study of patients with early (disease duration ≤1 year) RA. In all patients the self-reported date of symptom-onset was recorded. Clinical, laboratory and radiological assessments were performed at inclusion and after 1, 2 and 5 years of follow-up. These hands and feet X-rays (total number 2960, mean follow-up duration 4.3 years) were scored according to the Sharp-van der Heijde score by 2 readers. The between reader ICCs for total Sharp score at baseline and after two years were 0.93 and 0.94, respectively. At inclusion, no patient had got prior treatment with DMARDs or glucocorticoids. During follow-up 213 patients participated in a 2-year randomized study on low dose prednisolone as an addition to DMARD-therapy.

Defining the seasons
Seasons were defined according to meteorologists in the Netherlands and Sweden as spring starting on March 1st, summer on June 1st, autumn on September 1st and winter on December 1st.

Statistical analyses
Chi-Square tests were used to compare the proportions of patients. Radiographic scores were log-transformed to approximate a normal distribution. A multivariate normal regression analysis was used with the radiographic score as response variable; see ref13 In the Dutch cohort, adjustments were made for age, gender and treatment strategy. In the Swedish cohort, adjustments were made for age and participating in a corticosteroid study. Analyses were done using SPSS, versions 17.0 and 18.0 (SPSS Inc., Chicago, IL, USA), p values <0.05 were considered significant.

RESULTS

The patient characteristics are depicted in Table 1. 26.6% of the Dutch RA-patients had their onset of symptoms during the winter (Figure 1). Although this percentage was higher than that of the other seasons, the difference was not significant (p=0.56). In the Swedish RA-patients, 29.6% of the patients had symptom onset during the winter (Figure 1), which was significantly higher than the other seasons (p=0.005).

Subsequently we analyzed the association between the four meteorologically defined seasons and the progression of joint destruction. In the Dutch RA-patients, we did not observe that patients with a symptom onset in one of the four seasons had a different rate of progression of joint destruction compared to symptom onset in the other seasons (p=0.29) (see Figure 2A). Also in the Swedish RA-patients, no significant association between the
season of symptom onset and the severity of joint destruction over time was observed (p=0.46) (see Figure 2B).

Likewise, when comparing only two seasons namely the patients with symptom onset in summer or winter, no significant differences in progression of joint destruction were observed in both cohorts.

In a recent paper, Mouterde et al. reported a significant effect of a first symptom onset in winter and spring on erosions development during the first 12 months of follow-up. In their study, seasons were defined differently, namely winter = January 1–March 31, spring = April 1–June 30, summer = July 1–September 30 and autumn = October 1–December 31 (personal communication with professor B. Combe). Having learned this, we recoded our seasons in the same way in order to replicate the French findings. Performing the analyses over 7 years in the Dutch dataset, we obtained an association for disease onset in winter and radiographic joint destruction (p=0.02) Analyzing the 5-year follow-up data in the Swedish dataset revealed no significant association (p=0.89).

Table 1. Baseline characteristics of the Leiden EAC and the BARFOT patients

<table>
<thead>
<tr>
<th></th>
<th>Leiden (n=688)</th>
<th>Barfot (n=830)</th>
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<tbody>
<tr>
<td>Women, n (%)</td>
<td>462 (67.2)</td>
<td>538 (64.1)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>56.7 (15.7)</td>
<td>56.7 (15.4)</td>
</tr>
<tr>
<td>Symptom duration (weeks), mean (SD)</td>
<td>26.2 (22.4)</td>
<td>26.9 (13.8)</td>
</tr>
<tr>
<td>Swollen Joint Count (28 joints), mean (SD)</td>
<td>9.1 (6.9)</td>
<td>10.6 (5.6)</td>
</tr>
<tr>
<td>Anti-CCP2 positive, n (%)</td>
<td>349 (50.7)</td>
<td>418 (55)</td>
</tr>
<tr>
<td>CRP, mean (SD)</td>
<td>30.0 (34.4)</td>
<td>33.8 (37.7)</td>
</tr>
</tbody>
</table>

Figure 1. Percentage of RA-patients with symptom onset in each of the seasons in Dutch RA-patients and Swedish RA-patients
Several studies reported that season-related factors influence the onset of RA, though other studies challenged this.\textsuperscript{3,8,10} The interpretation of observed seasonal influences is often that RA may be triggered by for instance viral infections or different Vitamin D levels. A recent study observed that the season of symptom onset is also associated with erosive disease after 12 months and concluded that season related environmental factors are relevant for disease outcome.\textsuperscript{10} This is the only study evaluating the association of seasons with structural damage. Since erosiveness early in the disease is the most potent predictor for a progressive destructive disease course, we investigated seasonality in relation to long-term progression of joint damage, taking advantage of two large longitudinal datasets (total number of X-rays 6990, total number of patients 1473). Despite our finding that there was a tendency towards an effect of seasons on onset of RA symptoms, this was not accompanied by an effect on long-term outcome of RA.

In both cohorts, patients were included in a period when early and aggressive treatment strategies were not standard, and treatment adjustments were not target-driven. Hence the effect of treatment on the progression of joint destruction was supposed to be limited. In
addition, analyses were adjusted for differences in treatment strategies between patients. Furthermore, the effect of treatment on the progression of joint damage would not be different between patients with symptom-onset in different seasons. Altogether it seems unlikely that our negative findings are due to treatment effects.

In order to look for the discrepancies between our findings and those published by Mouterde et al., we asked the French group for their definition of seasons. In their analyses, winter started at January 1, which is dissimilar from a meteorological or astronomical definition of seasons. By this definition an association between winter and joint damage was observed in the Dutch but not in the Swedish RA-patients. Considering the overall negative comparisons and the number of tests performed, the result obtained in the Dutch patients could be a consequence of multiple testing.

It may be both a limitation and strength of the present study to analyze populations from two countries, although about 700 km apart, since one cohort might validate the results of the other. However, despite the fact that both the Netherlands and Sweden have a temperate climate, some seasonal differences between the two countries, e.g. in the amount of daylight, temperature and moisture, exist.

Seasonality should not be mixed up with weather effects. Irrespective of the degree of latitude, seasons vary from year to year in temperature, hours of sunshine or wetness. The present data do not allow drawing conclusions on occasional weather effects.

Studying seasonality and RA onset was not our main aim. Nonetheless, symptoms of Swedish RA-patients started slightly more often in winter. This may be by chance or a true finding. Vitamin-D levels are the lowest at the end of winter and are presumably lower in the Swedish than the Dutch population. Given the observation that the effect of seasons on RA onset was less pronounced in the Dutch patients, it is tempting to speculate about the role of vitamin D in RA onset. Nevertheless, other explanations are also possible. Importantly, if winter-related pathogenic factors affect the onset of RA, they do not seem to inflict on the severity of the disease course.

ACKNOWLEDGEMENTS

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REFERENCE LIST


