Clinical course and outcome of early rheumatoid arthritis

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Abstract We studied whether patients with seropositivity in early rheumatoid arthritis (RA) comprise a different clinical group than those with seronegativity. Four hundred seventeen patients with early RA according to the American College of Rheumatology criteria (disease duration less than 1 year) were retrospectively studied by analysis of demographic, clinical, laboratory, radiological, and therapeutic disease characteristics from the time of diagnosis until the end of the study period (1981–1999) using a data base. There were 248 seropositive patients and 169 seronegative patients with RA. No statistically significant differences were seen between the two groups before commencement of the study period in relation to age of disease onset, male:female ratio, and disease duration. However, seropositive patients showed longer medical follow-up. In addition, at disease onset, seropositive RA patients presented more frequently with symmetrical polyarthritis and small joint involvement than seronegative patients. The seropositive group also had more tender and swollen joints, weaker grip strength, and higher erythrocyte sedimentation and C-reactive protein rates during the follow-up period. In contrast, the seronegative group had less severe radiological findings and greater functional ability at the end of the study. In Greek patients with early RA, rheumatoid factor seems to be a predictor of more severe disease activity.

Keywords Early rheumatoid arthritis · Seropositive · Seronegative · Rheumatoid factor · Outcome

Introduction

Long-term studies of rheumatoid arthritis (RA) have shown that disease severity and outcome are influenced by a variety of socioeconomic factors [1, 2, 3, 4] such as race, gender, profession, education, and income. In addition, many clinical and laboratory parameters including age at onset, disease duration [3, 5, 6, 7], total joint count with tenderness and swelling [8, 9, 10, 11], and presence of rheumatoid nodules [3, 9, 11, 12, 13, 14], systemic manifestations, and radiological changes [3, 8, 15] may contribute to unfavorable prognosis. Finally, high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values [7, 8, 11, 14, 16, 17] and the rheumatoid “shared epitope” may also influence RA disease severity and outcome [18, 19, 20].

Rheumatoid factor (RF) has been widely used in studies and clinical practice as a laboratory index of prognosis among RA patients, defining a subgroup with differences in clinical manifestations and outcome [7, 9, 13, 14, 21].

The present study compares Greek seropositive and seronegative patients at the time of diagnosis and at the end of the study period. The findings showed significant differences in clinical characteristics, despite a similar course. The results confirm that serum RF is a significant factor affecting the progression and outcome of RA.

Materials and methods

The course and outcome of a total of 454 patients with early RA (length of disease prior to diagnosis less than 1 year and age greater than 16 years) [22] were studied retrospectively from a total of 1271 patients with RA followed up at the Rheumatology Department of the University Hospital of Ioannina, Greece, between 1981 and 1999. At the time of diagnosis, the patients fulfilled the 1958 American College of Rheumatology (ACR) criteria for definite and classic RA [23].

Patient records were reviewed and a standard form was used for all relevant clinical information on demographic, clinical, labora-
tory, radiological, and therapeutic disease characteristics from the time of diagnosis until the end of the study period. Treatment was initiated 1 or 2 weeks after diagnosis. Patients were followed up at standardized intervals (every month for the first 6 months and every 2–3 months thereafter) and this information was entered into a computer data base.

Patients with symptoms, signs, or a family history of psoriasis, inflammatory bowel disease, ankylosing spondylitis, Reiter's syndrome, polymyalgia rheumatica, or juvenile RA were excluded. The patients had not used disease-modifying antirheumatic drugs (DMARD) or corticosteroids before diagnosis and were divided into seropositive (IgM RF latex test ≥1:80) [24] or seronegative groups (latex test consistently negative for IgM RF in at least three serum counts). Patients with positive RF titers of 1:40 or fewer than three RF tests were excluded.

The following parameters were recorded for each patient at the time of diagnosis and at final follow-up: family history of RA, gender, age, duration of symptoms before diagnosis, length of follow-up, early morning stiffness (minutes), grip strength (mmHg with sphygmomanometer), distribution of the type of joints involved at the time of disease commencement (mono-, oligo-, or polyarthritis, small or large joint involvement, symmetrical or asymmetrical), number of painful and swollen joints, and number of patients with joint deformities and ankyloses at the end of the follow-up period.

All patients had X-rays of wrists, hands, and feet at the beginning and end of the study. These were reviewed using the Steinbrocker grading system (grades I–IV) [25] by the same examiner.

Laboratory parameters noted were CRP (in mg/ml), ESR (in mm/h), and the presence of anemia (Hb <13.5 mg% in men and <11.5 mg% in women).

Extra-articular manifestations during the disease period were also noted. These included vasculitis, serositis, episcleritis, rheumatoid nodules, secondary Sjögren's syndrome (SS), Raynaud's phenomenon, and carpal tunnel syndrome. Sjögren's syndrome was diagnosed after subjective xerostomia or xerophthalmia was confirmed by positive salivary gland biopsy (Tarpley grade >2) or reduced parotid gland flow and coexistence of a dry conjunctiva with a positive rose bengal and Schirmer's I tests [26]. Carpal tunnel syndrome was diagnosed clinically and confirmed by neurophysiological studies.

Patient functional ability was measured at the end of the study period using the ACR functional grading system (grades I–IV) [27], as were global evaluations by patient and physician on a grading scale of bad, medium, good, or very good. Finally, the number, type, and length of administration of DMARD given during the study were noted.

Student’s t-test, χ² test with Yates correction, analysis of variance (ANOVA), and least significant differences (LSD) test were applied when indicated.

### Results

Of the 1271 RA patients, 454 were diagnosed with early RA and a disease duration of less than 1 year. Nine of them had been treated before diagnosis with various DMARD and corticosteroids and were excluded from the study. In addition, 28 patients were lost from the follow-up. Thus, 417 fulfilled our criteria.

Table 1 shows the demographic characteristics of the subgroups with early RA. Prior to diagnosis, no statistical differences were seen between the two groups for gender, mean age, and disease duration. However, follow-up was significantly longer for the seropositive group ($P<0.0003$).

Figure 1 shows that seropositive patients' age at diagnosis peaked at 40–60 years and seronegative patients show a peak at 50–70 years. The latter also show more even distribution for the age at which the disease was diagnosed.

There were no differences in constitutional symptoms (fever, weight loss, morning stiffness) between the two groups at the time of disease commencement. There was also no difference between the two groups for positive family history for RA and symmetricality of the first

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Seropositive (n = 248)</th>
<th>Seronegative (n = 169)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>67</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>181</td>
<td>118</td>
<td>NS</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1.27</td>
<td>1.23</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>51.2 ± 14</td>
<td>52.6 ± 16.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean</td>
<td>16–83</td>
<td>16–84</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.6</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration before diagnosis (years)</td>
<td>5.1 ± 4.1</td>
<td>3.95 ± 3.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
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</tbody>
</table>

**Fig. 1** Graph showing patient ages at RA disease onset showing peaks at 40–60 years in seropositive patients and more even distribution with peaks at 50–70 years in seronegative patients.