Clinical significance of rheumatoid factor isotypes in seropositive arthritis

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Summary. In this cross-sectional study a comparison was made of rheumatoid factor (RF) isotypes in 203 RF positive patients with arthritis. Of these, 129 had rheumatoid arthritis (RA) and 74 a milder disease that would formerly have been classified as probable RA. The majority (74%) of the RA patients had elevations of two or three RF isotypes compared with only 34% of the patients with the milder form of arthritis. A striking feature was that combined elevation of IgM RF and IgA RF was found in 67% of the RA patients compared to only 20% of the patients with milder arthritis who most frequently had an isolated elevation of IgM RF (41%). RA patients with an isolated elevation of IgA RF were younger and had a shorter disease history than RA patients with an isolated elevation in IgM RF or a combined elevation of IgA RF and IgM RF. The prevalence of raised IgM RF was, furthermore, found to increase with age and disease duration. We concluded that a raised level of IgA RF is an adverse phenomenon in patients with seropositive arthritis while patients with an isolated increase in IgM RF may be expected to experience a relatively mild disease course.

Key words: Rheumatoid arthritis – Rheumatoid factor – Rheumatoid factor isotypes – ELISA

Introduction

Rheumatoid factors (RF) are autoantibodies that are predominantly directed against the Fc part of the immunoglobulin G (IgG) molecule. Raised levels of RF are frequently found in patients with rheumatoid arthritis (RA) but can also be found in other rheumatic conditions, infections and even in some apparently healthy individuals [1]. Furthermore, an increased prevalence of raised RF has been reported in symptom free members of families with multiple cases of RA [2]. RF is usually measured by agglutination techniques such as the Rose-Waaler and Latex methods. However, individual RF isotypes can now be determined by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay [3, 4]. The clinical usefulness of RF isotype specific measurements is currently being investigated [5–10]. Reports on the prevalence of raised IgM RF in RA have ranged from 30% to over 90% [10, 11] and even greater differences have been reported in the prevalence of IgG RF and IgA RF. These discrepancies may be due to differences in patient selection or to different methods for measuring and defining the upper limits of normal for the RF isotypes.

In this cross-sectional study we analyzed RF isotype elevations and patterns in RF positive patients with arthritis and their associations with diagnosis, disease severity, duration and age.

Materials and methods

Patients and samples. Patient selection was based on the presence of a clinical arthritis associated with a positive RF screening test [12] and an elevation of at least one RF isotype. Clinical information was obtained from the patients’ rheumatologists who filled in a structured questionnaire, including questions relating to diagnosis, treatment, age, sex, and disease duration.

Table 1. Clinical data on the study cohort

<table>
<thead>
<tr>
<th></th>
<th>Rheumatoid arthritis (n=129)</th>
<th>Milder arthritis (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.5 years (19–81 years)</td>
<td>45.3 years (16–85 years)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>(Females/males)</td>
<td>(95 F/34 M)</td>
<td>(60 F/14 M)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>11.6 years (6 months–48 years)</td>
<td>6.9 years (3 months–20 years)</td>
</tr>
<tr>
<td>Disease activity</td>
<td>1.84 ± 0.75 (Mean ± SD)</td>
<td>1.09 ± 0.50</td>
</tr>
<tr>
<td>Remitting drugs</td>
<td>82.9%</td>
<td>16.2%</td>
</tr>
</tbody>
</table>

* Gold, penicillamine, anti-malarials and cytotoxic drugs
duration and activity of the disease, bone erosions and drug therapy. Disease activity was given a score ranging from 0 to 3 (0 = no activity, 1 = mild, 2 = moderate and 3 = severe). The study cohort consisted of 203 RF positive patients; RA was diagnosed in 129, and 74 had a milder arthritis that would previously have been classified as probable RA [13]. Information is presented in Table 1 on age and sex distribution, disease duration, activity and the use of remitting drugs in the two groups.

RF assays. The ELISA procedure has been described in detail elsewhere [12]. Briefly, microtiter plates were coated with rabbit IgG and remaining protein binding sites were blocked with bovine serum albumen. Dilutions of test samples and serial dilutions of an internal standard were then incubated followed by aggregated rabbit IgG (40 μg/ml) to block any free binding sites for IgG on the solid phase bound RF. This procedure was found to minimize the interference due to IgM RF in this assay system (unpublished observations). Alkaline phosphatase (A.P.) conjugated mouse monoclonal anti-human light chain antibodies were used for detection of the RF in the screening assay but A.P.-conjugated anti-human IgM, IgG or IgA was used when individual RF isotypes were measured. After incubation with a p-nitrophenyl phosphate substrate the absorbance was read at 405 nm. Intra-assay variability was 6% and inter-assay variability was approximately 20%. Results were expressed in arbitrary units per ml (AU/ml) according to an internal standard. The distribution of RF isotype levels was measured in 100 randomly selected adults and RF values of above the 95% cut-off level (25 AU/ml) were considered to be raised.

Statistical analysis. The data were analyzed with the chi-square test (with Yates correction for expected frequencies of less than five) and the Mann-Whitney U-test. The level of significance was set at P < 0.05.

Results

Table 2 shows the prevalence of single or combined RF isotype elevations in controls and in the study cohort. Increased levels of two or three RF isotypes were observed in the great majority (73.6%) of the RA patients compared with only 33.8% of those with the milder disease (P = 0.0001). It was also striking that 66.7% of the RA patients had a combined elevation of the IgM RF and IgA RF isotypes while this pattern was only observed in 20.3% of the patients with the milder form of arthritis (P = 0.0001) whose predominant pattern was an isolated elevation of IgM RF (40.5%).

Table 4. Percentage of patients with elevated RF isotypes in relation to age. N.S. = not significant

The higher prevalence of IgA RF in the RA patients was not associated with a longer disease duration or older age. On the contrary, as shown in Table 3, RA patients with isolated elevations of IgA RF were significantly younger and had a shorter disease course than RA patients with raised IgM RF (with or without concomitant elevation of IgA RF). A similar trend was observed in the patients who had the milder arthritis. Thus, the prevalence of raised IgM RF was found to increase with age in both groups of patients but a corresponding phenomenon was not observed in relation to the IgG RF and IgA RF isotypes (Table 4). The prevalence of raised IgM RF also increased progressively with disease duration in

Table 3. Comparison of mean age and disease duration in relation to RF findings in patients with RA and milder arthritis

Table 4. Percentage of patients with elevated RF isotypes in relation to age. N.S. = not significant