Concise Report

Relationship between rheumatoid arthritis and *Mycoplasma pneumoniae*: a case–control study

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**Objective.** Rheumatoid arthritis (RA) has a complex and multifactorial aetiology. Infectious agents could start this disease. The majority of the characteristics of this infirmity can be observed in chronic arthritis produced by mycoplasmas in animals. In this study the association between *Mycoplasma pneumoniae* and RA has been evaluated.

**Methods.** A case–control study was performed. Sera taken from 78 RA patients and from 156 controls were analysed to ascertain the levels of immunoglobulin G (IgG) against *M. pneumoniae*. Other variables, like age, gender, work status, history of pneumonia, etc., were recorded in a questionnaire.

**Results.** The presence of antibodies against *M. pneumoniae* was associated with RA (odds ratio = 2.34, \( P < 0.001 \)).

**Conclusions.** The results suggest that *M. pneumoniae* could be a cofactor in the pathogenesis of RA; however, more studies need to be done.

**Key words:** Case–control studies, Rheumatoid arthritis, Mollicutes, *Mycoplasma pneumoniae*, ELISA.

Rheumatoid arthritis (RA) has a complex and multifactorial aetiology. The agent/agents that cause the illness still remain unknown; however, it has been shown that genetic risk (histocompatibility antigens, especially HLA-DR4) and immunoregulatory factors (autoimmunity) play an important role in the disease [1]. Some authors implicate *Mycoplasma* as a cofactor in inflammatory articular illness [2–13, especially in RA [3, 12, 14–18]. Many characteristics of RA can be observed in chronic arthritis produced by *Mycoplasma* such as *M. capricolum* subsp. *capricolum*, *M. hyosynoviae*, *M. hyorhinis* and *M. synoviae* in different animal species [18, 19]. Mycoplasmas (Class Mollicutes) can affect host cell growth and morphology, and they are also able to alter metabolic, immunological and biochemical functions [20]. They also effectively evade host immune responses and can interact synergistically with other infectious agents [15].

Haier et al. [15] detected, using the polymerase chain reaction (PCR), several *Mycoplasma* species in blood leucocytes of patients suffering from RA. Johnson et al. [17] detected *M. fermentans* in 31 of 34 samples from RA patients. This result contrasts with the results obtained by van der Heijden et al. [21] and Gilroy et al. [18], who detected bacterial DNA amplicons in synovial samples from only 5 RA patients from a total of 26 and from only 6 RA patients from 35, respectively.

Most of the animal arthritogenic mycoplasmas also cause respiratory infections. It is known that *M. pneumoniae*, a producer of atypical pneumoniae in humans, induces respiratory and non-respiratory sequelae, including arthritis [3]. The proportion of *M. pneumoniae* respiratory infections that develop arthritis is unknown [19]. Davis et al. [22] isolated this micro-organism from joint effusion of a patient with pneumonia and polyarthritis.

One of the problems in trying to classify RA as an infectious illness is the lack of epidemiological evidence [23]. With this study, we have tried to determine if there is any relationship between *M. pneumoniae* and RA.

**Materials and methods**

**Design of the study**

The design is a case–control study matching one case to two controls with respect to age and gender.

**Target population**

Adults from Gran Canaria Island (Spain) attached to the ‘Hospital Insular’ (half of the island population).

**Cases**

Cases (\( n = 78 \)) were out-patients at Hospital Insular and diagnosed with RA, fulfilling the revised criteria of the American Rheumatism Association [24]. The patients were examined by two rheumatologists. Local ethics committee approval and informed patient consent were obtained.

**Controls**

Controls (\( n = 156 \)) were selected from blood donors and pre-operative admissions. The absence of an autoimmune illness case-history was confirmed by checking their hospital records.

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Specimen collection and serological method
Blood samples were collected. The sera were analysed for the presence of antibodies against *M. pneumoniae*. IgG titres were measured using the enzyme-linked immunosorbent assay (ELISA) *M. pneumoniae* (Wampole) and a Spectra-Shell analyser, following the manufacturers’ instructions.

Questionnaire
Interviews were carried out to study different variables. Details of age, gender, civil state, employment and any history of pneumonia were obtained. Only the cases were asked the following specific questions relating to the illness: family history of RA, the number of years with RA and age of onset of RA symptoms. Radiological stage, measuring structural joint damage as previously described [25] and serum IgG rheumatoid factor were recorded from the medical records.

Statistical analysis
Categorical variables were reported as frequencies and percentages and numerical variables as means, range and standard deviations (s.d.). Both odds ratios (OR), crude and adjusted, were estimated by logistic regression models using the conditional likelihood and 95% confidence intervals (CI) were computed [26]. A test was calculated in the multivariate model adjusted by age and gender. The statistical analysis was performed with SPSS statistical program version 11.0 for the univariate analysis and the R package for the multivariate analysis.

Results
Characteristics of the cases and controls and corresponding OR (crude and adjusted), 95% CI and the *P* value

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 78), n (%)</th>
<th>Controls (n = 156), n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>53.17</td>
<td>52.19</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>13.94</td>
<td>13.96</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>22–81</td>
<td>21–81</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (16.7)</td>
<td>26 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (83.3)</td>
<td>130 (83.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>57 (73.1)</td>
<td>108 (71.5)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>13 (16.7)</td>
<td>16 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Widower/er</td>
<td>5 (6.4)</td>
<td>20 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>3 (3.8)</td>
<td>7 (4.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>22 (28.6)</td>
<td>60 (39.5)</td>
<td></td>
</tr>
<tr>
<td>Pensioner/retired</td>
<td>30 (39.5)</td>
<td>16 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>22 (28.6)</td>
<td>75 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 (2.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>1 (1.3)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><strong>A previous episode of pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (12.8)</td>
<td>12 (7.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68 (87.2)</td>
<td>139 (92.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Antibodies against <em>M. pneumoniae</em></strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive titre</td>
<td>42 (53.8)</td>
<td>49 (31.4)</td>
<td>0.227 1.7</td>
</tr>
<tr>
<td>Negative titre</td>
<td>36 (46.2)</td>
<td>107 (68.6)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
The aetiology of RA remains unknown. Cases presented higher concentrations of immunoglobulins G, A and M than the appropriate controls. An infection can be an obvious reason for an increase in the serum immunoglobulins, as a result of a specific immunostimulation or a non-specific polyclonal B-cell activation [23]. Bacterial and viral infections have been suggested as arthritogenic stimulants. The failure to isolate these microorganisms could be due to their disappearance as a result of action of the immune system. However, the humoral response produces specific serum antibodies, which are easily detected.

Horowitz et al. [16] found no significant difference in the prevalence of serum antibodies to *M. fermentans* between patients with RA, those with other arthritis, and healthy controls. In the present study, an association between the variable antibodies against *M. pneumoniae* and RA was statistically significant (*P* < 0.001), indicating that people who have had contact with this micro-organism are about twice as likely to suffer from RA. However, there are no significant differences between cases and controls who had suffered from pneumonia, maybe because infections with this organism can cover a spectrum from flu-like symptoms to overt pneumonia.

Cytadherence is considered to be the initial step in the virulent process of pathogenic mycoplasmas. *M. pneumoniae* has adhesins that have an extensive sequence homology to mammalian structures. This molecular mimicry could generate autoreactive antibodies [20]. It has also been suggested that a superantigen is present in human mycoplasmas such as *M. arthritidis* (a producer of arthritis in rodents) which triggers autoimmune and other inflammatory pathologies [27].
The results from this study point to the hypothesis that Mycoplasma may be associated with RA; however, it cannot be demonstrated whether mycoplasmas are cofactors or whether they produce a secondary infection or occur more in those with abnormal immune systems who have RA. Information that supports the Mycoplasma hypothesis is the successful use of minocycline in RA treatment and the knowledge that mycoplasmas are sensitive to tetracyclines and that mycoplasmas support the hypothesis with abnormal immune systems who have RA. Information that they produce a secondary infection or occur more in those be demonstrated whether mycoplasmas are cofactors or whether Mycoplasma may be associated with RA; however, it cannot

### References


### Key messages

- The probability that RA is present is higher in people with antibodies against *M. pneumoniae* than without them.