Original Article

Correlation of Demographic and Clinical Characteristics with Rheumatoid Factor Seropositivity in Rheumatoid Arthritis Patients

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Abstract

***Background*: The rheumatoid factor (RF) blood test is the most commonly adopted test for the diagnosis of rheumatoid arthritis (RA). RA patients who are seropositive for RF might face a greater likelihood of developing more aggressive symptoms.**

***Methods*: Our goal was to study the demographic and clinical characteristics, as well as their correlation with RF seropositivity, among a series of 80 RA patients aged ≥ 18 years who attend Hospital Universiti Sains Malaysia (HUSM).**

***Results*: Of the 80 RA patients included in this study, 66 (82.5%) were female and 14 (17.5%) were male. No significant associations between RF seropositivity and demographic and/or clinical characteristics or other laboratory investigations were observed, including gender, morning stiffness, individual joint involvement (from multiple sites of the body), and erythrocyte sedimentation rate (ESR) measurement. However, a significant association between RF seropositivity and patients aged ≥ 50 was found (P = 0.032).**

***Conclusion*: RF seropositivity was found to be more common in much older RA patients.**

Keywords: *autoimmune disease, rheumatoid arthritis, rheumatoid factor, erythrocyte sedimentation rate*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which the articular symptoms occur in a systemic pattern. The condition affects millions of people worldwide, with a prevalence ranging from 0.5% to 1% of the general population (1–3). The risk factors for RA include genetic susceptibility factors, gender, age, smoking, infectious agents, hormonal factors and ethnic factors (4, 5). It has been proposed that there is an association between the HLA-DRB1 shared epitope alleles and anti-citrullinated protein antibodies (ACPA) in three Asian populations, namely the Malay, Chinese and Indian ethnicities from Malaysia (6), which suggests that genetic susceptibility factors play an important role in the pathogenesis of RA (7).

RA manifestations can involve any of the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints and metatarsophalangeal (MTP) joints, as well as the joints in the wrist and knee (8). The large joints include the shoulders, elbows, knees and ankles, while the small joints include the MCP, PIP, MTP, thumb interphalangeal joint and wrists (9). The clinical presentation of RA varies, although an insidious onset of pain accompanied by symmetric swelling of the small joints is the most common symptom (8).

One of the characteristics of RA is the presence of distinct autoantibodies in the sera of patients (10). Rheumatoid factor (RF) was one of the first autoantibodies to be discovered in the sera of RA patients (11). RF is a specific autoantibody directed towards the IgG molecule (12). The IgM rheumatoid factors (IgM-RF) are the major RF species found in RA and they can be detected in 60–80% of established cases of RA and 50–60% of RA patients in the early stages of the disease (13, 14). Additionally, RF can be detected in healthy individuals several years prior to the onset of clinical RA (15, 16).

RF has also been found in several other diseases, including systemic lupus erythematosus, mixed connective tissue disease and primary Sjögren's syndrome, as well as in non-autoimmune conditions such as chronic infections and old age (13, 17), which indicates that RF could be an outcome of non-specific immune activation (18).

The aim of this study is to provide data regarding the frequency of RF autoantibodies in a local cohort of RA patients (n = 80), as well as to correlate its presence with demographic and clinical parameters and laboratory investigations.

Materials and Methods

Patients and data collection

We retrospectively reviewed the records of 80 RA patients who were diagnosed between 1988 and 2015. All the patients met the 2010 American College of Rheumatology (ACR) classification criteria for the disease (9). The following clinico-demographic data were retrieved from the Medical Records Unit at HUSM: age, age at onset of RA, gender, serological biomarker (RF), laboratory parameter (ESR) and clinical symptoms including morning stiffness, joint swelling and the pattern of joints affected by RA. Joint involvement here refers to any swollen or tender joints identified during the examination by the attending rheumatologist.

Immunoassays

The patients' RF status was obtained using the latex agglutination test (RF Direct Latex; VEDALAB, France) and the results was reported qualitatively. The presence of a visible agglutination was considered to be a positive indicator of RF. Elevated ESR levels were defined as ≥ 15 mm/hr and ≥ 20 mm/hr in male and female patients, respectively.

Statistical analysis

All data entry and statistical analyses were performed using IBM© SPSS© Statistics version 22. We performed χ^2-square analyses to compare the clinico-demographic characteristics with the presence of RF autoantibodies in RA patients at the time of initial diagnosis. In all the analyses, a two-tailed $P < 0.05$ was considered to be statistically significant.

Results

Most of the RA patients were aged over 50 years (n = 58/80; 72.5%). The RA cohort consisted of 66 (82.5%) females and 14 (17.5%) males, with a ratio of 4.7:1. The mean and median age of the cohort were 54.8 years and 57 years, respectively, while the mean and median age of the cohort at the onset of RA were 48 years and 50.5 years, respectively.

All the 80 RA patients exhibited joint symptoms (Table 1). The involvement of both the small and large joints was the most common finding (n = 47/80; 58.8%), while the numbers of small and large joints individually affected by RA were 22 (27.5%) and 11 (13.8%), respectively. The clinical symptoms recorded were morning stiffness (n = 42/80; 52.5%) and joint swelling (n = 28/80; 35.0%). The joints most frequently involved were the hand (n = 55/80; 68.8%), knee (n = 30/80; 37.5%), wrist (n = 24/80; 30.0%), ankle (n = 22/80; 27.5%), shoulder (n = 21/80; 26.3%) and elbow (n = 17/80; 21.3%). In terms of the immunological investigation, the result of the latex agglutination test for RF was slightly higher for positive reactions (n = 41/80; 51.3%). The demographic and clinical characteristics of the cohort at the time of RA onset are presented in Table 1.

The associations of RF seropositivity with demographic and clinical characteristics, as well as other laboratory investigations including gender, age, individual joint involvement (from multiple sites of the body), morning stiffness, joint swelling and ESR measurement, are summarised in Table 2. In our cohort, the ESR varied from 2–150 mm in a period of one hour (mean: 47 mm/hr). No significant differences were observed between the gender groups in terms of the correlation with RF seropositivity.

The most important result of our study was the significant correlation of RF seropositivity with older patients (aged ≥ 50 years; P = 0.032) (Table 2), which suggests that RF seropositivity increased with age in our cohort of RA patients.

Table 1. Demographic and clinical characteristics of RA patients at disease onset

Characteristics	Descriptions
Female/Male	66/14
Female: Male ratio	4.7:1
Age, years	54.8 (13.9)[a]
Age at RA onset, years	48 (13.2)[a]
ESR (mm/hr)	47.4 (30.8)[a]
RF- positive, *n* (%)	41 (51.3)
RF- negative, *n* (%)	39 (48.7)
Age < 50, *n* (%)	22 (27.5)
Age ≥ 50, *n* (%)	58 (72.5)
Pattern of joint involvement, *n* (%)	
Ankle	22 (27.5)
Elbow	17 (21.3)
Knee	30 (37.5)
Shoulder	21 (26.3)
Hand	55 (68.8)
Wrist	24 (30.0)
Small joints	22 (27.5)
Large joints	11 (13.8)
Both joints	47 (58.8)
Clinical symptoms, *n* (%)	
Morning stiffness	42 (52.5)
Joint swelling	28 (35.0)

[a]Mean (SD)

Discussion

In this study, we presented data concerning the demographic and clinical characteristics, as well as their association with RF, among a local cohort of RA patients (n = 80). As anticipated, the cohort of RA patients were predominantly female, which is similar to findings from other parts of the world, including the USA (19), United Kingdom (20), China (21), France (22), Japan (23) and Syria (24). The dysregulation of the oestrogen level might explain why women are much more likely to develop RA than men, whereas androgens may play a suppressive role in the development of the disease (2). Prolactin is essential for the normal function of the immune system. In females, it stimulates the growth of the mammary glands and promotes lactation (25); however, elevated levels of prolactin may contribute to the severity of RA (26).

In our cohort, the majority of RA patients were female (82.5%), which is consistent with other Malaysian cohorts of RA patients (27–29) that showed a similar proportion of female patients (83.8–91.3%). In our study, 41 of the 80 patients (51.3%) tested positive for RF using the latex agglutination methodology, while another study involving Malaysian RA patients reported a higher proportion of patients (n = 85 out of 100; 85.0%) testing positive for RF using the ELISA kit methodology (27). This indicates that methods employing distinct principles (e.g. agglutination versus ELISA) to assay RF could, at least partially, contribute to differential RF detection. In terms of the ESR values, our cohort demonstrated an ESR of 2–150 mm in one hour (mean: 47 mm/hr), which is similar to the ESR value obtained from other local RA patients (n = 80) (29) that ranged from 3 to 120 mm/hour, with a mean of 51.6 mm/hour.

The most significant finding in our study was related to the RF seropositivity associated with patients aged 50 years old and above. It has been acknowledged that the RF is positive in 10–20% of individuals over 65 years old (30). In our cohort, 34 out of 58 RA patients (58.6%) aged ≥ 50 years tested positive for RF. However, a previous study by Gomez and colleagues (28) demonstrated that there were no differences between the patients' age and RF seropositivity in a series of 147 RA patients from the Selangor and Negeri Sembilan states of Malaysia (located in the middle part of Peninsular Malaysia), which suggests that RF seropositivity is more common in older Malaysian RA patients from the northern states of Peninsular Malaysia (e.g. Kelantan).

The prevalence of positive reactions has been shown to be consistently higher in aged persons than in young persons (13, 31). Chronic infection, which is typically more frequent and more severe in older individuals (32), is known to be associated with a high frequency of RFs in RA. Several infectious agents have been implicated in RA, including Epstein-Barr virus, proteus and mycoplasma (1). Another study reported that Malaysian RA patients exhibited a higher prevalence of bronchopulmonary infection when compared to non-RA patients (33).

No individual pattern of joints affected by RA was found to be correlated with RF. However, our study showed that the hand joints were the site most commonly affected, followed by the knee and wrist. According to a previous study (29), the majority of RA patients had bilateral

Table 2. Association of demographic and clinical characteristics with RF

Variables	Presence of RF		*P*-value[a]
	Yes *n* (%)	No *n* (%)	
Demographic	34 (51.5)	32 (48.5)	0.918
Female	7 (50.0)	7 (50.0)	
Male			
Age, years			
< 50 years old	7 (31.8)	15 (68.2)	
≥ 50 years old	34 (58.6)	24 (41.4)	0.032
Pattern of joint involvement			
Ankle			
Yes	11 (50.0)	11 (50.0)	
No	30 (51.7)	28 (48.3)	0.890
Elbow			
Yes	6 (35.3)	11 (64.7)	
No	35 (55.6)	28 (44.4)	0.138
Knee			
Yes	16 (53.3)	14 (46.7)	
No	25 (50.0)	25 (50.0)	0.773
Shoulder			
Yes	8 (42.1)	13 (61.9)	
No	33 (19.5)	26 (44.1)	0.160
Hand			
Yes	25 (45.5)	30 (54.5)	
No	16 (64.0)	9 (36.0)	0.124
Wrist			
Yes	13 (54.2)	11 (45.8)	
No	28 (50.0)	28 (50.0)	0.733
Clinical symptoms			
Morning stiffness			
Yes	23 (54.8)	19 (45.2)	
No	18 (47.4)	20 (52.6)	0.509
Joint swelling			
Yes	13 (46.4)	15 (53.6)	
No	28 (53.8)	24 (46.2)	0.527
Laboratory parameters			
ESR (mm/hr), male			
< 15	0 (0)	3 (100.0)	
≥ 15	7 (63.6)	4 (36.4)	0.051
ESR (mm/hr), female			
< 20	3 (37.5)	5 (62.5)	
≥ 20	31 (53.4)	27 (46.6)	0.397

[a] χ^2-square test, *P*-value < 0.05 is significant.

pain or stiffness in the small joints of the hand. Indeed, hand involvement is a typical early manifestation of RA (8). It has been suggested that the joints most commonly affected are those with the highest ratio of synovium to articular cartilage, with the wrists nearly always being involved, as well as the PIP, MCP, knee, ankle and elbow (34, 35).

It was observed that most of the patients experienced pain, swelling and stiffness in multiple joints. The clinical features of synovitis were particularly apparent during the morning, when morning stiffness in and around the joints was a typical sign of RA (8). Although there is no single laboratory test used to diagnose RA, several laboratory abnormalities can be

measured. Abnormal values for the systemic inflammation tests are the most common humoral features of RA (8). Further, ESR was among the most commonly used acute phase reactant for measuring the disease's activity (4).

In terms of treatment, anti-tumour-necrosis-factor (TNF) agents such as infliximab, etanercept and adalimumab are frequently used to treat RA patients due to their well-established effectiveness (36). The patients achieve reduced disease activity and functional disability when such agents are used in combination with methotrexate (MTX) (37–39). Studies have shown that RA patients who are seropositive for RF demonstrated a reduced response to anti-TNF agents (40–42). For RA patients who are unresponsive to anti-TNF agents, the therapeutic antibody rituximab is adopted (43). Two independent phase III clinical trials have shown that RF-positive patients experienced superior outcomes when treated with rituximab when compared to RF-negative patients (44, 45). Moreover, in MTX-naïve RA patients who are positive for RF, treatment with rituximab plus MTX was more likely to achieve improvements in clinical outcomes when compared to RF-negative patients (46). Further observational studies are required to determine whether our cohort of RF-positive patients are more likely to be unresponsive to anti-TNF agents and/or exhibit a significantly better response to regimens involving rituximab when compared to RF-negative patients.

Conclusion

Our retrospective analysis of this local cohort of RA patients showed that RF seropositivity was associated with older patients, which suggests that older Malaysian RA patients from the northern states of Peninsular Malaysia are more likely to demonstrate RF seropositivity.

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Conflict of Interest

None

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Authors' Contribution

Conception and design: MAO, WKK
Analysis and interpretation of the data: MAO, WKK
Drafting of the article: MAO, WKK
Critical revision of the article for important intellectual content: MAO, WKK
Final approval of the article: MAO, WKK, WSWG, NKY
Provision of study materials or patients: WSWG, NKY
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