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ORIGINAL ARTICLE

Comparative Analyses of Serological Biomarkers and Disease Characteristics between Elderly-onset and Younger-onset Rheumatoid Arthritis

RAJALINGHAM S[1*], SYAHRUL SAZLIYANA S[1], ABDUL WAHAB A[2], MAHADZIR H[1]

[1]Department of Medicine, [2]Department of Microbiology and Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

ABSTRAK

Penyakit rheumatoid arthritis (RA) boleh terjadi pada bila-bila masa selepas usia 16 tahun. Tujuan kajian ini adalah untuk membandingkan golongan pesakit RA yang mendapat penyakit ini selepas usia 60 tahun (EORA) dengan pesakit yang mendapat penyakit ini pada usia yang lebih muda (YORA), dari segi klinikal dan serologi. Sejumlah 69 pesakit perempuan EORA dan 82 pesakit perempuan YORA telah menyertai kajian ini. Data berkenaan umur semasa diagnosis, aktiviti penyakit semasa diagnosis, ubat-ubatan dan tempoh penyakit dikumpul dengan merujuk kepada rekod pesakit. Sampel darah kesemua subjek diuji dengan ujian serum 'anti-cyclic citrulinated peptide' (anti-CCP), IgA 'rheumatoid factor' (RF), IgM RF dan IgG RF. Kerosakan sendi dan ketidakupayaan fizikal ditentukan melalui 'Modified Sharp Score' (MSS) dan 'Health Assessment Questionnaire-disability Index' (HAQ-DI). Walaupun tempoh masa penyakit dan kekerapan seropositiviti tidak berbeza dengan signifikan antara kedua-dua kumpulan, kumpulan YORA telah mencatatkan aktiviti penyakit yang lebih tinggi dan ketara semasa diagnosis penyakit RA (p=0.009). Selaras dengan penemuan ini, kumpulan YORA mempunyai kerosakan sendi yang lebih teruk (skor MSS sebanyak 17.49±19.04 berbanding 10.04±12.79). Kumpulan YORA telah mempunyai paras IgA RF dan anti-CCP yang jauh lebih tinggi dengan nilai p sebanyak 0.035 and 0.002. Keputusan kajian ini mencadangkan bahawa kumpulan YORA mempunyai kaitan dengan penyakit RA yang lebih serius, kerosakan sendi yang lebih teruk dan paras anti-CCP dan IgA RF yang lebih tinggi.

Kata kunci: antibodi, berusia, rheumatoid arthritis, serologi

Address for correspondence and reprint requests: Associate Professor Dr. Rajalingham Sakthiswary. Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91456097 Email: sakthis5@hotmail.com

ABSTRACT

The onset of rheumatoid arthritis (RA) may occur any time after the age of 16 years. The purpose of this study was to compare the clinical and serological differences between elderly onset RA (EORA); which is begins at the age of 60 and above, with younger onset RA (YORA). A total of 69 EORA and 82 YORA female patients were enrolled in this study. Data on medications, disease duration, age at onset, disease activity at onset and laboratory parameters were collected by reviewing the medical records. All patients had their blood samples taken for serum anti-cyclic citrulinated peptide (anti-CCP), IgA rheumatoid factor (RF), IgM RF and IgG RF. Besides, the subjects were assessed for their radiographic joint damage based on Modified Sharp Score (MSS) and functional disability based on the Health Assessment Questionnaire-disability Index (HAQ-DI) scores. Despite comparable disease duration and frequency of seropositivity, the YORA group had significantly higher disease activity at onset of the disease (p=0.009). In keeping with this finding, the YORA group had more severe joint damage based on radiographic assessment (MSS scores of 17.49±19.04 versus 10.04±12.79). The YORA group had significantly higher levels of IgA RF and anti-CCP with p-values of 0.035 and 0.002, respectively. Our findings suggest that YORA is associated with more severe disease, worse radiographic joint damage and higher levels of anti-CCP and IgA RF.

Keywords: aged, antibodies, rheumatoid arthritis, serology

INTRODUCTION

Rheumatoid arthritis (RA) is a heterogenous disease with a variable age at onset of the disease. Although its peak incidence is in the fourth and fifth decades of life, the onset of RA may occur anytime from adolescence to geriatric age (Kerr 2004). The definition of elderly-onset RA (EORA) or late-onset RA (LORA) in the literature has typically used either 60 (Mueller et al. 2014; Tutuncu et al. 2006) or 65 years (Olivo et al. 1996) as the cut-off age. We decided to use the lower cut-off age of 60 and above to define EORA in this study. The United Nations has historically used the age of 60 and above to define an "older" person (Daily Briefing 2019). The reported prevalence of EORA using a cut off of 60 years in a South Korean nationwide cohort study was 15.33% (Cho et al. 2012)

With increasing life span and expanding ageing populations in many countries across the world, EORA has gained more importance in the recent decades, especially from the 1980s (Reinhard & Calkins 1993). There has been debates on whether younger onset RA (YORA); onset before 60 years, and EORA represent different diseases or the same disease entity

with a different expression (Soubrier et al. 2010). Despite the growing importance, EORA has not gained the attention it deserves and rarely been investigated in detail.

Due to the heterogeneity and inconsistencies in the conclusions from previous studies which compared EORA with YORA, this study was developed to compare the clinical, laboratory and serological characteristics between Malaysian female EORA and YORA patients. This study is an extension of our previous work on serological and laboratory profiling of Malaysia RA patients (Sakthiswary et al. 2016; Sakthiswary et al. 2014).

MATERIALS AND METHODS

Study Design

This was a cross-sectional study which involved female rheumatology outpatients using convenient sampling; which was conducted from January to December 2015 at the Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The study proposal was reviewed, approved and funded by the UKMMC Ethics & Research Committee (Study Code FF code IP-2014-053).

Sample Size Calculation

The estimated sample size was a total of 139 RA patients with a 10% population proportion and 95% confidence interval as well as 5% margin of error. The following formula was used to calculate the sample size: $z^2p(1-p)/€^2$ (z=z score of 1.96 for a confidence interval of 95%, p=population proportion, €=margin of error)

Study Population

Patients with RA were recruited from the Rheumatology Clinics of UKMMC. The following were the inclusion criteria for the RA patients: (i) Patients who fulfilled The American College of Rheumatology (ACR) 2010 criteria for RA (Aletaha et al. 2010); (ii) Patients aged 18 years and above; (iii) Patients who were able to provide written or verbal consent. The ACR 2010 classification criteria for RA is the latest criteria which is used extensively in clinical practice and research trials. A score of 6 and above fulfills the criteria for RA based on 4 domains which include joint involvement, serology results, duration of symptoms of more than 6 weeks and abnormal erythrocyte sedimentation rate (ESR) and or C-reactive protein (CRP) test(s) (Aletaha et al. 2010).

The following were the exclusion criteria: (i) Pregnant patients as radiographs were contraindicated due to the risk of radiation to the fetus; (ii) Overlap syndrome or co-existence of other autoimmune diseases such as Systemic Lupus Erythematosus, psoriasis and Systemic Sclerosis; (iii) Patients with active infection; (iv) Patients with malignancy. Autoimmune diseases, infections and malignancies may cause raised levels of inflammatory markers i.e. ESR and CRP.

Data Collection

Data on medications, disease duration, age at onset, disease activity at onset and laboratory parameters were collected by reviewing the medical records of the RA patients. All patients had their blood samples taken for serum anti-cyclic citrulinated peptide (anti-CCP), IgA rheumatoid factor (RF), IgM RF and IgG RF. Besides, the hands and feet radiographs were taken for scoring using Modified Sharp Score (MSS). The Health Assessment Questionnaire-disability Index (HAQ-DI) scores were determined by interviewing the subjects. The interview was conducted by a single interviewer to avoid inter-interviewer variability.

Study Parameters

Disease Activity Score in 28 joints (DAS 28)

We used DAS 28 to determine the disease activity of RA. This scoring system is used worldwide in RA clinical trials (Makinen et al. 2005a). The variables used to calculate DAS 28 were; (i) number of swollen joints; (ii) number of tender joints; (iii) ESR and (iv) the patient's global assessment (Prevoo et al. 1995). DAS 28 score of 3.2 and above indicates moderate to severe disease activity (Makinen et al. 2005b). The European League against Rheumatism (EULAR) response criteria was used to determine the treatment response i.e. good, moderate or non-responder. A good responder had a DAS 28 of ≤3.2 with improvement in DAS 28 of >1.2 from baseline. A non-responder had a DAS28 improvement of ≤0.6 or DAS28 of >5.1 with improvement between 0.6 to 1.2. The rest of the subjects were classified as moderate responders.

Modified Sharp Score (MSS)

We used MSS to assess the radiographic joint damage in this study. This radiographic scoring system looks into erosions and joint space narrowing (JSN) of hands and feet. The scoring was performed by a single radiologist who was blinded to the subjects. In MSS, in each hand, there are 16 areas for erosions and 15 areas for joint space narrowing, and, in each foot, 6 areas for erosions and 6 areas for joint space narrowing. The erosion score per joint of the hands can range from 0 to 5 depending on the severity. The maximum MSS score is 448 (Pincus et al. 1997).

Health Assessment Questionnaire-disability Index (HAQ-DI)

We used HAQ-DI to assess the functional capacity of the subjects involving the fine movements of the upper extremity and locomotor activities of the lower extremity. The questionnaire consisted of 20 questions pertaining to common daily activities such as dressing, eating, walking and hygiene. Higher scores indicate more severe disability (0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty ; and 3 = unable to do). A score of 1 indicated significant (moderate to very severe) functional disability (Bruce & Fries 2003).

Serological Tests

The IgM, IgA and IgG RF isotypes were tested using an indirect solid-phase enzyme-linked immunosobent assay (ELISA) which involved the binding of Fc fragments of highly purified human IgG to microwells from *Dade Behring,* Marburg, Germany. The quantitative analysis for the RF isotypes were calibrated according to the tests kit manual. The procedure was carried out in triplicate. RF concentrations of above 15 IU/mL were considered positive. The anti-CCP test was performed using a commercially available ELISA kit (*Axis-Shield*, Dundee, UK). The upper normal limit of 5 U/mL was based on the manufacturer's recommendations.

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA). The continuous variables (age, DAS 28, MSS, HAQ-DI, disease duration etc.) were tested for normality using Kolmogorov Smirnov test. Data with normal distribution were analysed using independent t-test and expressed as mean standard deviation (SD). Categorical data, on the other hand, were analysed using chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient and Diseases Characteristics

A total of 69 EORA and 82 YORA patients were enrolled in this study. Only female subjects were recruited to achieve a more homogenous study population. The mean age of the subjects with EORA was 67.19±2.49 years whereas for YORA was 31.93±5.10 years. Table 1 summarises the clinical characteristics of the subjects. Despite comparable disease duration and frequency of seropositivity, the YORA group had significantly higher disease activity at onset of the disease (p=0.009). The inflammatory markers were higher in this group. In keeping with this finding, the YORA group had more severe joint damage based on radiographic assessment (MSS scores of 17.49±19.04 versus 10.04±12.79).

There were no significant differences between the groups in terms of functional disability, number of DMARDs, prednisolone dose and treatment response. Majority of the subjects in both arms were on a single DMARD which was mostly methotrexate. The other conventional DMARDs used in this study were sulfasalazine, hydroxychloroquine and leflunomide. A significantly higher percentage of YORA subjects (42.68%) required advanced therapies such as tumour necrosis factor and janus kinase inhibitors to control the disease.

In this study cohort, more than half of the patients achieved good treatment response. Although there was no statistically significant difference, it is noteworthy that the YORA group had double the percentage (10.98%) of non-responders compared to the EORA group (5.80%).

Serological Markers

The most commonly tested RF in clinical practice is IgM RF. However, in

Table 1: Comparison of disease characteristics between EORA and YORA

Parameter	EORA (n=69)	YORA(n=82)	p value
Age (years)*	67.19 ± 2.49	31.93 ± 5.10	<0.050
Ethnicity, n (%)			
Malay	47 (68.12)	61 (74.39)	0.599
Chinese	14 (20.29)	15 (18.29)	
Indian	8 (11.59)	6 (7.32)	
Disease duration (years)*	8.06 ± 5.04	8.70 ± 3.63	0.365
DAS28 at onset*	3.29 ± 1.37	3.96 ± 1.68	0.009
RF positive at onset	47 (68.11)	62 (75.61)	0.306
Anti CCP (U/ml) titre*	84.52 ± 117.97	151.14 ± 138.02	0.002
IgA RF titre (IU/ml)*	24.15 ± 39.54	43.14 ± 64.82	0.035
IgM RF (IU/ml) titre*	68.58 ± 97.65	72.74 ± 93.28	0.789
IgG RF (IU/ml) titre*	64.36 ± 66.01	70.88 ± 69.58	0.558
ESR at onset (mm/hr)*	54.20 ± 20.50	67.04 ± 23.60	0.001
CRP at onset(mmol/L)*	1.33 ± 1.37	3.79 ± 8.11	0.019
No. of DMARDS			
1	45 (65.21)	41(50.00)	0.106
2	16 (23.19)	32 (39.02)	
3	8 (11.59)	9 (10.98)	
On biologics & tsDMARD	12 (17.39)	35 (42.68)	0.008
Prednisolone dose (mg)*	2.83 ± 3.32	2.77 ± 3.02	0.920
Treatment Response			
Good	50 (72.46)	54 (65.86)	0.487
Moderate	15 (21.74)	19 (23.17)	
None	4 (5.80)	9 (10.98)	
MSS*	10.04 ± 12.79	17.49 ± 19.04	0.006
HAQ-DI*	1.47 ± 0.87	1.58 ± 0.71	0.397

HAQ-DI=Health Assessment Questionnaire Disability Index; DAS 28=28 joint based Disease Activity Score; RF=rheumatoid factor; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; MSS=Modified Sharp Score; tsDMARD=targeted synthetic DMARD

Data presented as either counts (percentages) or mean ± SD*

our previous study we have identified IgA RF as a predictor of more severe disease (Sakthiswary et al. 2014). The YORA group had significantly higher levels of IgA RF and anti-CCP with p-values of 0.035 and 0.002, respectively. The IgM and IgG RFs were comparable between the 2 groups. Of note, the mean titres for all 4 autoantibodies were higher among the YORA group.

DISCUSSION

This study highlights the differences between EORA and YORA in a multi-ethnic Malaysian population. We found that YORA was associated with more severe and aggressive disease, clinically and biochemically. There are several studies in the literature comparing EORA and YORA with variable and inconsistent findings.

The discordance in the findings is multifactorial. The cut off age used to define EORA in one study was as low as 55 years (Ranganath et al. 2005). The remaining studies used either 60 years or 65 years (Mueller et al. 2014; Narayanan et al. 2001; Olivo et al. 1996; Spinel-Bejarano et al. 2013). Genetic and socioeconomic factors may contribute to the discrepancies in the findings.

In keeping with our findings, Huscher et al. (2013) and Spinel-Bejarano et al. (2013) reported that YORA patients had higher disease activity and were less frequently in remission. Studies by Lance & Curran (1993) and Mueller et al. (2014) on the contrary, found the EORA patients to have more aggressive and destructive disease. Teoh et al. (2014) and Ranganath et al. (2005) mentioned that there were no differences between EORA and YORA with regard to baseline disease severity. The baseline disease activity is influenced by the time interval between the onset of symptoms and medical or rheumatology consultation. Delayed presentation often results in higher baseline disease activity (Wan et al. 2020). It is tempting to speculate that countries with efficient elderly care and support system will have EORA patients with lower baseline disease activity due to early presentation. This notion, however, lacks evidence derived from formal studies.

The use of advanced therapies (biologic and targeted synthetic DMARDs) was significantly higher among our YORA patients. Apart from clinical indication, there are other factors which determined the use of these medications. Advanced therapies which tend to be expensive, are not fully subsidised in Malaysia. Hence, affordability plays an important part in determining the access and use of these medications. Many YORA patients tend to be employed with medical coverage of advanced therapies, unlike EORA patients.

The YORA patients in our study had more severe joint damage despite the comparable disease duration with the EORA patients. This finding is expected given that the YORA group had a more active disease. However, the above finding was in contrast with most studies in the literature which compared YORA with EORA. Mueller et al. (2014) revealed that disease activity and radiographic joint damage were higher in EORA at onset but the radiographic progression at 5 years were similar between both the groups. In general, studies have consistently reported that disease activity had a parallel course with radiographic joint damage (Curtis et al. 2019; Movahedi et al. 2020).

This is the only study which has compared the levels of RF serotypes between YORA and EORA. Therefore, we were unable to make a comparison with other published studies. The mean titres of all 4 autoantibodies were higher in the YORA group, although only the differences in IgA RF and anti-CCP levels reached statistical significance. Along these lines, Mueller et al. (2014) and Spinel-Bejarano et al. (2013) reported higher percentage of seropositive disease for both RF and anti-CCP among YORA. RFs and anti-CCPs are produced by B cells. At the

cellular level, ageing affects expression of B-cell markers and B-cell responses (Frasca & Blomberg 2011). Depletion in B cells with age may account for the lower levels of autoantibodies, although the precise mechanism is unclear. Unlike inflammatory markers and cytokines, RF serotypes and anti-CCP levels tend not to change with treatment or disease activity. Mota et al. (2009) reported that RFs remain stable over a 3-year follow-up period. Hence, these autoantibodies are used for diagnostic and prognostic purposes without serial testing. In this study, there were no confounders for the levels of RF serotypes and anti-CCP.

We acknowledge the limitations of our study. A longitudinal study design is more accurate in capturing the differences between YORA and EORA, especially in terms of assessment of radiographic joint damage. Prospective studies enables scoring of the joints at fixed time intervals from the time of diagnosis for all subjects. Although YORA had higher disease activity and joint damage, the functional disability based on HAQ-DI scores were comparable between the 2 groups. Many EORA patients had other comorbidities which may contribute to functional limitation such as cataract, peripheral neuropathy or osteoarthritis.

In conclusion, our findings suggest that YORA is associated with more severe disease, worse radiographic joint damage and higher levels of anti-CCP and IgA RF.

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