Scientific
Research

Increased IgG Rheumatoid Factor-Positivity in the Asian Rheumatoid Arthritis Patients Irrespective of Ethnicity

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ABSTRACT

Aim of Work: Initial observations implied IgG rheumatoid factor (RF) to be common among Malaysian rheumatoid arthritis (RA) patients. We tested this hypothesis and used a multiethnic RA cohort (Malays, Chinese and Indians) to investigate whether the IgG RF predominance might be genetically or environmentally determined. Patients and Methods: 556 serum samples comprising 171 patients classified as RA according to the 1987 ACR criteria, 60 patients with other rheumatic diseases and 325 non-rheumatic controls were tested for IgG RF, IgM RF and anti-CCP by ELISA. The findings were then tested in a larger RA case-control cohort (n = 1844). Results: IgG RF predominated over IgM RF in all the investigated ethnic groups. The sensitivity, specificity, and diagnostic accuracy of IgG RF (55.6%, 91.2% and 80.2%, respectively) were superior compared to IgM RF, but comparable to anti-CCP. IgG RF was however, also increased in the Malaysian controls, but the IgG RF superiority over IgM RF was still apparent after cutoff adjustment according to the 1987 ACR criteria. Autoantibody levels did not differ between the three ethnic groups. The Receiver Operating Characteristics (ROC) curves showed larger areas under the curves for IgG RF (0.826) and for anti-CCP (0.867) than for IgM RF (0.737). Review of the literature showed consistently higher sensitivity for IgG RF in studies of Asian RA patients as compared to Caucasian and African-American studies. Conclusion: Increased frequency of IgG RF-positive in RA populations with different genetic background living in Malaysia argues for an environmental factor selectively amplifying the IgG RF response.

KEYWORDS

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting 0.5% to 1% of the global population [1-3]. It is characterized by chronic inflammation, which generally leads to progressive joint destruction and consequent disability and reduction of quality of life if not treated promptly and adequately [1-3]. Recent evidence suggests that early intervention is crucial in preventing irreversible joint damage. Thus, it is important to diag-

nose RA at an early stage [4,5].

Until very recently, the diagnostic classification of RA has been based on the 1987 American College of Rheumatology (ACR) revised criteria, which includes rheumatoid factor (RF), clinical and radiological criteria [6]. RFs can be detected in 60% to 80% of the patients with RA [2,7]. IgM is the most frequently studied RF isotype and also most commonly measured in clinical laboratories. It is also the most common RF isotype in Caucasian RA populations [8,9]. Some studies have implicated IgA RF as especially associated with extra-articular RA and

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with erosive RA [10]. Simultaneous detection of IgM and IgA RF has been shown to be highly specific for RA in Iceland [8]. While IgG RF has a lower specificity than the other isotypes in the Caucasian RA populations [8,9], it has been implicated in RA patients with nodules [11], vasculitis [12,13] and hyperviscosity syndrome [14]. Generally, much less is known about the importance of IgA and IgG RF in chronic disease [7].

Initial observations in our laboratory implied IgG RF to be common among Malaysian patients with RA. As the Malaysia population consists of three major ethnic groups with different genetic backgrounds, but sharing the same general environment, we carried out this study to test the hypothesis that the prevalence of IgG RF might be increased in Malaysia and to investigate whether any increase in IgG RF would be general or limited to the major population of Malaysia, the Malays. We also investigated the presence of anti-cyclic citrullinated peptide antibody (ACPA) by using the anti-cyclic citrullinated peptide (anti-CCP) antibodies kits, as ACPA have been included together with RF in the serology domain of the new EULAR/ACR RA classification criteria [15].

2. Patients and Methods

A total of 556 subjects were enrolled in the study between July 2005 and July 2007. Serum samples were obtained from 171 consecutively enrolled patients with RA, 60 patients with other rheumatic diseases and 325 non-rheumatic controls. All serum samples were stored at −20˚C until assayed. These three sample groups were used as the initially investigated cohort (henceforth named the first set). An independent set of serum samples were collected from 886 patients with RA and 958 controls from the Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA) case-control study and were used for replication (second set) of the initial findings. In the replication study population, the median disease duration for RA was one year (inter quartile range, IQR = 2 years). The total number of 1844 individuals in this replication study is part of the 1079 RA cases and 1470 healthy controls, included in recently published paper [16], where RF isotypes were not investigated.

Table 1 shows the baseline demographic characteristics of the subjects recruited for this study. In the first set study, all the patients with RA and other rheumatic diseases were recruited from three government rheumatology clinics in Malaysia. All RA cases were diagnosed by rheumatologists according to the 1987 ACR classification criteria [6]. The disease duration for RA at the time of blood sampling was stratified into two groups: <2 years and >2 years. Radiological findings were recorded

Table 1. Baseline demographic characteristics of rheumatoid arthritis, other rheumatic diseases and non-rheumatic controls.

	RA	Other rheumatic diseases	Non-rheumatic controls
Initially investigated cohort (first set)			
Samples size (n)	171	60	325
Females (%)	150 (87.7)	49 (81.7)	273 (84.0)
Age: mean ± SD (years)	47.8 ± 11.6	40.2 ± 13.3	46.2 ± 11.5
Ethnicity (n) (%)			
Malay	92 (53.8)	37 (61.2)	179 (55.1)
Chinese	31 (18.1)	12 (20.0)	62 (19.1)
Indian	39 (22.8)	8 (13.3)	67 (20.6)
Others	9 (5.3)	3 (5.0)	17 (5.2)
Disease duration (n = 171)			
<2 years (%)	124 (72.5)	-	-
>2 years (%)	47 (27.5)	-	-
Radiographic characterization (n = 117)			
Erosive (%)	38 (32.5)		
Non-erosive (%)	79 (67.5)		
Replication cohort (second set)			
Samples size (n)	886	-	958
Female (%)	752 (84.9)	-	862 (89.9)
Age: mean ± SD (years)	48.2 ± 11.7	-	47.7 ± 11.4
Ethnicity (n) (%)			
Malay	355 (40.1)	-	603 (62.9)
Chinese	191 (21.6)	-	122 (12.7)
Indian	278 (31.4)	-	178 (18.6)
Others	62 (6.9)	-	55 (5.7)

RA: rheumatoid arthritis; SD: standard deviation.

as absence or presence of hand joint erosions. Radiographic erosion data was available for 117 of 171 (68.4%) of the patients with RA. Out of these, 73 of 117 (62.4%) were diagnosed within less than two years of first joint symptoms.

The diagnosis in the rheumatological control group were systemic lupus erythematosus (SLE; n = 28), psoriatic arthritis (PSA; n = 9), osteoarthritis (n = 8), gouty arthritis (n = 3), mixed connective tissue disease (MCTD; n = 3), reactive arthritis (n = 2), scleroderma (Sc; n = 2), palindromic RA (n = 1), spondylarthritis (n = 1), systemic vasculitis (n = 1), tendinitis (n = 1) and primary Sjögren's syndrome (PSS; n = 1). Diagnoses were based on clinical signs and symptoms, as well as laboratory and radiological findings. Patients with incomplete or uncertain diagnosis were not included.

The 325 non-rheumatic controls in the first set were recruited from the hospitals where the RA cases were recruited and comprised voluntary individuals who accompanied the patients and hospital staff (n = 286), and patients without any autoimmune diseases (dengue fever patients, n = 10 and cardiovascular disease patients, n = 29). We used a common control group by pooling the rheumatic controls and non-rheumatic controls when comparing the diagnostic utility of RF and anti-CCP antibodies for RA. Only the healthy controls (n = 286) were used for the adjustment of the IgG and IgM RF cutoffs according to the 1987 ACR criteria [6], which defines >95% specificity compared to healthy controls. The study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia. All the participants were informed about the research, and written consents were obtained.

3. Laboratory Methods

Anti-CCP antibodies were measured using the anti-CCP second generation enzyme-linked immunosorbent assay (ELISA) kits (Immunoscan RA Mark 2, Euro-Diagnostica, Malmö, Sweden). Samples with results <25 U/mL were defined as negative. IgG and IgM RF were determined by IBL-rf_AGM ELISA kits (IBL, Hamburg. Germany). The analysis of IgG RF poses inherent technical problems not applicable to other RF isotypes. If human IgG is used for coating, the detection anti-human IgG antibody will not only detect the bound IgG RF, but also the coating antigen. In the present study, the RF assay kits used the highly purified Fc fragment of human immunoglobulin (IgG) for coating according to the manufacturer. In the initial evaluation, samples with results ≤15 IU/ml were defined as negative according to the manufacturer's recommendations. If the preceding evaluations, Malaysian-adjusted cutoffs were then established as the 96th percentile of Malaysian healthy controls according to the 1987 ACR classification criteria which request >95% specificity as compared to healthy controls (the newly adjusted-cutoffs were 12 IU/ml for IgM RF and 20 IU/ml for IgG RF). All assays were performed according to the manufacturer's instructions.

4. Statistics

χ^2-test (and Fisher's exact test when appropriate) was used to compare proportions. Mann-Whitney's U test was used to compare autoantibody levels in seropositive subjects from the three ethnic groups. Sensitivity and specificity were expressed in percentages. To evaluate the overall diagnostic utilities of serological markers for RA, the diagnostic accuracy was calculated as ([number of test-positive RA subjects] + [number of test-negative

subjects in control groups])/(total number of subjects in the RA and control groups). When used according to the manufacturer's instructions, the anti-CCP2 kits employed do not deliver quantitative data below the company-defined cutoff, and the assumption of a linear relationship between 0 U/ml and 25 U/ml has been used to calculate the quantitative values for anti-CCP < 25 U/ml, both in cases and controls, in order to perform ROC analyses. Statistical analyses have been conducted using SPSS 20.0 statistical software. ROC curves were constructed using the MedCalc software.

5. Results

5.1. Prevalence of Autoantibodies in RA, Other Rheumatic Diseases and Non-Rheumatic Controls

The overall prevalence of IgG RF was 55.6% among RA cases, but also noticeable high among rheumatic (25.0%) and non-rheumatic controls (5.8%; Table 2). The prevalence of IgM RF was 36.8%, 10% and 2.8% in RA, other rheumatic diseases and non-rheumatic controls, respectively. After adjusting the cutoff to 20 IU/ml for IgG RF and 12 IU/ml for IgM RF, respectively (the 96th percentile of the 286 geographically matched healthy subjects according to the 1987 ACR criteria [6]), the increase IgG RF positivity was still apparent (46.6%) in comparison with 40.4% IgM RF-positive RA cases (Table 3).

Anti-CCP was detected in 98 of 171 (57.3%) patients with RA, comparable to IgG RF. Three of 60 (5.0%) patients in other rheumatic diseases and 7 of 325 (2.3%) non-rheumatic controls were anti-CCP positive.

IgM RF was found in 32.3% of RA patients with disease duration <2 years, and in 48.9% of patients with long-standing disease, a difference reaching borderline significance (p = 0.044). For the other investigated autoantibodies there were no significant differences between patients with short and long disease duration. There were also no differences in proportions of autoantibodies between patients with and without radiographic erosions (data not shown).

In agreement with a number of earlier studies, the specificity of anti-CCP (97.1%) was superior to that of IgG RF (91.2%) and IgM RF (96.1%), in the first set of RA cases compared to the combined control groups. To evaluate the overall diagnostic utility of serological markers for RA, the diagnostic accuracy was calculated. The diagnostic accuracy was highest for anti-CCP, intermediate for IgG RF and lowest for IgM RF (Table 3).

5.2. Replication Study

We performed the autoantibody measurements in the second set to replicate the findings of increased IgG

Table 2. The number and percentage of patients with RA, and other rheumatic diseases, and non-rheumatic controls with positive titer for anti-CCP, IgG RF and IgM RF.

Diagnosis	All	IgG RF positive (%)	IgM RF positive (%)	Anti-CCP positive (%)
Rheumatoid arthritis (RA) (% sensitivity)				
Initially investigated cohort (first set)	171	95 (55.5)	63 (36.8)	98 (57.3)
Replication cohort (second set)	886	471 (53.2)	457 (51.6)	581 (65.6)
Other rheumatic diseases (total)	60	15 (25.0)	6 (10.0)	3 (5.0)
SLE	28	6 (21)	2 (7)	0 (0)
Psoriatic arthritis	9	4 (44.4)	1 (11.1)	1 (11.1)
Osteoarthritis	8	0 (0)	0 (0)	0 (0)
Gouty arthritis	3	1 (33.3)	0 (0)	0 (0)
MCTD	3	1 (33.3)	1 (33.3)	0 (0)
Reactive arthritis	2	0 (0)	0 (0)	0 (0)
Scleroderma	2	2 (100)	1 (50.0)	1 (50.0)
Palindromic rheumatism	1	0 (0)	0 (0)	0 (0)
Spondyloarthritis	1	0 (0)	0 (0)	0 (0)
Systemic vasculitis	1	0 (0)	0 (0)	0 (0)
Tendinitis	1	0 (0)	0 (0)	0 (0)
Primary Sjögren's syndrome	1	1 (100)	1 (100)	1 (100)
Non-rheumatic controls				
Initially investigated cohort (first set)	325	19 (5.8)	9 (2.8)	7 (2.3)
Replication cohort (second set)	958	73 (7.6)	44 (4.6)	27 (2.8)
Healthy individuals among non-rheumatic controls (first set)	286	17 (5.9)	8 (2.3)	6 (2.1)
All rheumatic and non-rheumatic controls (first set)	385	34 (8.8%)	14 (3.6%)	10 (2.6%)
Overall specificity (first set)	-	91.2%	96.1	97.1%

RA: rheumatoid arthritis; anti-CCP: anti-cyclic citrullinated peptides; RF: rheumatoid factor; SLE: systemic lupus erythermatosus; MCTD: mixed connective tissue disease.

Table 3. Occurrence of IgG RF, IgM RF, anti-CCP autoantibodies in three Asian ethnic groups with RA.

Tests	All RA patients (n = 171)				Malay RA patients (n = 92)			Chinese RA patients (n = 31)			Indian RA patients (n = 39)		
	Sensitivity (%)	Specificity (%)[*]	AUC	Diagnostic Accuracy (%)	Sensitivity (%)	Specificity (%)[*]	AUC	Sensitivity (%)	Specificity (%)[*]	AUC	Sensitivity (%)	Specificity (%)[*]	AUC
IgG RF	55.6	91.2	0.826	80.2	57.6	91.2	0.825	61.3	91.2	0.881	48.7	91.2	0.803
IgG RF (ACR cutoff)	(46.6[**])	-	-	-	(46.7[**])	-	-	(51.6[**])	-	-	(41.0[**])	-	-
IgM RF	36.8	96.1	0.737	77.9	35.9	96.1	0.718	45.2	96.1	0.768	38.5	96.1	0.774
IgM RF (ACR cutoff)	(40.4[***])	-	-	-	(38.0[***])	-	-	(51.6[***])	-	-	(43.6[***])	-	-
Anti-CCP	57.3	97.1	0.867	85.1	53.3	97.1	0.873	61.3	97.1	0.869	61.5	97.1	0.874

AUC: Area under curve; [*]All groups were compared to the same control group, as detailed in Materials and Methods. [**]After adjustment for the cutoff to 20 IU/mL, the 96th percentile for the 286 healthy controls, according to 1987 ACR criteria (6). [***]After adjustment for the cutoff to 12 IU/mL, the 96th percentile for the 286 healthy controls, according to 1987 ACR criteria (6).

RF-positive found in the first set, using independent serum samples from 886 RA cases and 958 control subjects. Also in this study, which in contrast to the first set consisted mainly (>95%) of early RA cases (<2 years of symptom at diagnosis), more patients were positive for IgG RF (53.2%) than for IgM RF (51.6%; **Table 4**).

5.3. Superiority of IgG RF over IgM RF in All Three Ethnic RA Populations

When patients were stratified according to ethnicity, the proportions of autoantibody positive RA cases did not differ significantly for IgG or IgM RF between any of the three ethnic groups, and the higher sensitivity for IgG RF

Table 4. Occurrence of RF isotypes and anti-CCP in different published studies, grouped after geographical descent.

Paper	Geographical descent	RA patients (n, % females)	IgA RF (%)	IgG RF (%)	IgM RF (%)	Anti-CCP (%)	Healthy (H) or disease (D) controls (n, % females)	IgA RF (%)	IgG RF (%)	IgM RF (%)	Anti-CCP (%)
Caucasian populations											
Vallbracht, 2004 [9]	Germany	295, 80.3	150 (50.8)	129 (43.7)	196 (66.4)	190 (64.4)	H154, 54.5	7 (4.5)	7 (4.5)	11 (7.1)	1 (0.6)
Jonsson, 1998 [8]	Iceland	70, 79	42 (60)	31 (44)	50 (71)	-	D 205, 85	14 (7)	24 (12)	14 (7)	-
Nell-Duxneuner, 2010 [26]	Austria	200[*], 73	(29)	(14)	(45)[**]	(41)	-	-	-	-	-
African American											
Mikuls, 2006 [25]	USA (African Americans)	195, 81	(65)	(39)	(70)	(62)	H87, 82 D97, 90	(5)[***]	(5)[***]	(5)[***]	11(6)
Singwe-Ngandedu [27]	African (Cameroon)	56, 95	47 (84)	-	43 (77)	46 (82)	H51	0 (0)	-	4 (8)	
Asian populations											
Singh, 2010 [24]	India	119, 85.7	44 (36.9)	50 (42)	57 (47.9)	46 (50)[****]	H26	0 (0)	1 (3.8)	0 (0)	0 (0)
Ahmed, 2010 [17]	Iraq	53, 88.7	(41.5)	(83)	(62.3)	-	-	-	-	-	-
Gomez, 2011 [19]	Malaysia	147, 87.8	31 (21.1)	71 (48.3)	78 (53.1)	100 (68.0)	-	-	-	-	-
Idem Malay		45, 93.3	8 (17.8)	27 (60.0)	28 (62.2)	33 (73.3)	-	-	-	-	-
Idem Chinese		50, 82	9 (18.0)	23 (46.0)	26 (52.0)	33 (66.0)	-	-	-	-	-
Idem Indian		52, 88.5	14 (26.9)	21 (40.4)	24 (46.2)	34 (65.4)	-	-	-	-	-
Initial study (First set)	Malaysia	171, 87.7	-	95 (55.6)	63 (36.8)	98 (57.3)	H325, 84 D60. 81.7	-	34 (8.8)	15 (3.9)	10 (2.6)
Idem Malay		92, 82.6	-	53 (57.6)	33 (35.9)	49 (53.3)		-	-	-	-
Idem Chinese		31, 77.4	-	19 (61.3)	15 (45.2)	19 (61.3)		-	-	-	-
Idem Indian		39, 92.3	-	19 (48.7)	15 (38.5)	24 (61.5)		-	-	-	-
Malaysia-adjusted ACR 1987 cutoffs		171, 87.7	-	79 (46.6)[*****]	69 (40.4)[*****]		H325, 84	-	9 (4)	8 (4)	-
Replication study (Second set)	Malaysia	886, 84.9	-	471 (53.2)	457 (51.6)	581 (65.6)	H958, 89.9	-	73 (7.6)	44 (4.6)	27 (2.8)
Idem Malay		355, 84.8	-	180 (50.7)	173 (48.7)	224 (63.1)		-	44 (7.3)	26 (4.3)	18 (3.0)
Idem Chinese		191, 84.3	-	96 (50.3)	96 (50.3)	126 (66.0)		-	9 (7.4)	3 (2.5)	3 (2.5)
Idem Indian		278, 84.3	-	155 (55.8)	162 (58.3)	186 (66.9)		-	15 (8.4)	11 (6.2)	4 (2.2)

[*]Early arthritis. [**]45% IgM RF positive using cutoffs 50 IU/ml; 55% IgM RF positive using cutoffs 20 IU/ml [30]. [***]Calculated as 95th percentile of the control groups. [****]92 patients investigated for anti-CCP. [*****]Calculated as 96th percentile of the healthy control groups.

as compared to IgM RF was evident among Malay, Chinese and Indian RA cases. For the Chinese RA patients the same sensitivity (61.3%) was found both for IgG RF and anti-CCP (**Table 3**). There was however, no difference in autoantibody levels when the RA cases with a positive test result for IgG RF, IgM RF or anti-CCP were compared between the ethnic groups (data not shown).

For the comparison of the diagnostic utility of each marker in RA, we additionally undertook ROC analyses, and calculated the areas under the curves (AUC; **Figure 1** and **Table 3**). The overall AUC of anti-CCP (0.867) was rather similar to IgG RF (0.826) but considerably higher than for IgM RF (0.737). When individual ROC-curves were constructed for the three ethnic groups of RA cases, the finding of a generally higher AUC value of IgG RF as compared to IgM RF could be demonstrated in all three ethnic groups. For the Chinese RA cases the AUC for IgG RF even surpassed the AUC value for anti-CCP. AUC values for the individual ROC curves are detailed in **Table 3**.

5.4. Occurrence of Anti-CCP in RF-Negative RA

We also evaluated the utility of anti-CCP in RF-negative RA. Overall, anti-CCP was detected in 38.2% and 22.4% IgM RF and IgG RF-negative RA cases, respectively. Anti-CCP was found in more than 35% of the IgM RF-negative RA among all ethnic groups, and the corresponding figures were lower for IgG RF-negative RA cases in all the investigated ethnic groups, again stressing the difference between IgM and IgG RF in these Asian populations (**Table 5**).

6. Discussion

The diagnostic and prognostic values of anti-CCP antibody determination, alone or associated with RFs have been evaluated carefully [17-22], but the distribution of seroprevalence across different populations has not been reported. The present study shows that the presence IgG RF-positive RA cases were consistently higher than the occurrence of IgM RF in all three investigated ethnic groups with RA in Malaysia. Also, in a replication study involving early RA cases, IgG RF was more common than IgM RF (53.2% versus 51.6%). We also compared with previous studies which have displayed data showing IgG RF levels higher or close to IgM RF levels in other Asian RA populations (**Table 4**).

Significant differences exist among RF test kits and the reliability of some assays is questionable [23]. When RF isotype kits from the same manufacturer used in this study was assessed in a study of 295 German RA cases, the awaited IgM RF preponderance commonly seen in Caucasian studies was evident (IgM RF 66.4%, IgA RF
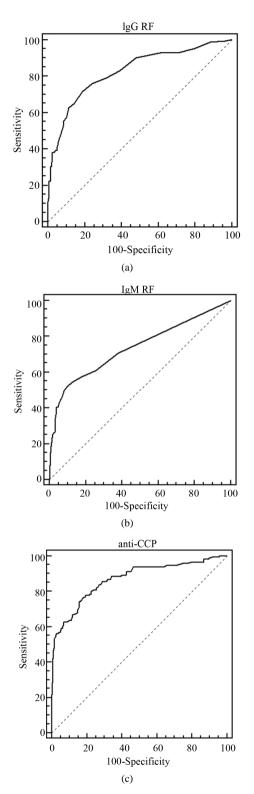

Figure 1. The receiver operator characteristic (ROC) curves for IgG RF, IgM RF and anti-CCP autoantibodies in the diagnosis of RA in Malaysian population. (a) IgG RF with area under ROC curve of 0.826; (b) IgM RF with area under ROC curve of 0.737; and (c) anti-CCP with area under ROC curve of 0.867.

Table 5. The occurrence of anti-CCP antibodies among IgG RF-negative or IgM RF-negative RA patients.

Anti-CCP-positive RA patients	Anti-CCP-positive and IgM RF-negative RA patients, n (%)	Anti-CCP-positive and IgG RF-negative RA patients, n (%)
All (n = 98)	39 (39.8)	22 (22.4)
Malay (n = 49)	19 (38.8)	8 (16.3)
Chinese (n = 19)	5 (35.7)	3 (15.8)
Indian (n = 24)	10 (41.7)	8 (33.3)
Mixed ethnicity (n = 6)	5 (83.3)	3 (50.0)

RA: rheumatoid arthritis; anti-CCP: anti-cyclic citrullinated peptides; RF: rheumatoid factor.

50.8% and IgG RF 43.7%) [9], with data very similar to those obtained in other studies performed in European RA populations (Table 4), thus ruling out any inconsistency in the behavior of the diagnostic laboratory reagents used in our investigation.

In all Asian studies where three RF isotypes have been investigated, the lowest sensitivities are described for IgA RF, with considerably higher or comparable sensitivities both for IgM RF and IgG RF. An example of a strong predominance of IgG RF (83%) over IgM (62%) and IgA RF (42%) in Iraqi RA patients was reported by Ahmed and coworkers [17]. In a study on Indian RA patients IgG RF was almost as common as IgM RF (42% vs 48%), whereas IgA RF has a lower sensitivity (37%) [24]. Very recently, a somewhat smaller Malaysian study showed a frequency for IgG RF-positive that almost equaled the frequency for IgM RF-positive (48.3% vs. 53.1%), whereas only 21.1% were IgA RF-positive [19]. In contrast, all studies on non-Asian RA populations show the maximal sensitivity for IgM RF, followed by IgA RF and with the lowest sensitivities for IgG RF [8,9,25,26]. Intriguingly, while data on African American RA patients from the USA show figures similar to the European data (RF positivity: IgM RF > IgA RF > IgG RF) [25], Singwe-Ngandeu *et al*. reported higher prevalence of IgA RF (84%) followed by IgM RF (77%) in 56 African RA patients living in Cameroon [27]. Thus, our current findings and the differences in RF isotypes distribution observed in African RA patients living both in the USA and Cameroon arguing for an environmental factor triggering RF isotype distribution.

The pathological significance of IgG RF is uncertain. In Swedish pre-RA patients, where especially IgA RF appears years before the onset of RA, IgG and IgM RF appear much later [22,28]. This is in contrast to pre-SLE patients, where elevated pre-SLE IgG RF is more closely associated to the later appearance of arthritis, and also appears earlier than IgM RF [29]. In that study, IgA RF was not investigated.

The limitation of our present study is the lack of data on IgA RF. Our choice of which RF isotypes to investigate in both the first and second study set was influenced by earlier experience from routine investigations of Malaysian RA patients. Although we have found it useful to investigate IgM RF and IgG RF but not IgA RF, the preponderance of IgG RF in Asia, both as compared to other RF isotypes in the same RA populations, and as compared to IgG RF in non-Asian populations, has not been highlighted before. In future studies of RF isotype distributions in Malaysia we intend to also include IgA RF.

7. Conclusion

In conclusion, our findings imply a possible equally important role of IgG RF and IgM RF in all the three ethnic groups of Malaysian RA patients. This finding, together with earlier studies which also show high levels of IgG RF in different Asian and Iraqi RA populations but not in RA populations from Europe or in African Americans or in Cameroon Africans, imply the existence of environmental factor(s) which may promote the development of IgG RF in Asia, especially in RA populations.

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