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BRIEF REPORT

Latitude gradient influences the age of onset in rheumatoid arthritis patients

Cesar Ramos-Remus · Gabriela Sierra-Jimenez · Kenneth Skeith · Francisco J. Aceves-Avila · Anthony S. Russell · Robert Offer · Juan E. Olguin-Redes · Joanne Homik · Lourdes Sanchez · Adriana Sanchez-Ortiz · Gregorio Navarro-Cano

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Abstract The mean age of rheumatoid arthritis (RA) onset is around 50 years as reported in several clinical trials involving Caucasian patients. However, clinical observations suggest that Mexican RA patients' disease is initiated at a younger age. The objective of the study was to assess whether the age of onset of RA is different in Mexican and in Canadian RA patients. Certified rheumatologists from Canada and Mexico directly interviewed consecutive RA patients attending their clinics regarding the date patients first noticed a swollen joint. None of the participant rheumatologists were aware of the primary aim of this exploratory study at the time of the interviews. Data was gathered from 161 Mexican (91% women) and 130 Canadian (77% women) RA patients collected by three rheumatologists in each country. Duration since disease onset was not different within countries (mean 95% confidence interval [CI] for differences −10 to 16 years, p=0.12 for Canadians, and −6 to 10 years, p=0.26, for Mexicans). However, there was a significant difference between the two countries. Mexicans patients on average developed RA almost 12 years younger than Canadians (95% CI for difference 9 to 15 years, p<0.001). Frequency distribution showed that 35.5% of Canadians but only 4% of Mexicans had the onset of the disease after the age of 55 (all p<0.001). It appears that RA begins at a much younger age in Mexican than Canadian patients. If this were confirmed after controlling for different confounders and biases, it would have important societal, economic, and therapeutic implications.

Keywords Disease onset · Etiology · Geography · Latitude · Rheumatoid arthritis

C. Ramos-Remus · G. Sierra-Jimenez · F. J. Aceves-Avila · A. Sanchez-Ortiz
Department of Rheumatology, Hospital de Especialidades del Centro Medico Nacional de Occidente, IMSS, Guadalajara, Mexico

C. Ramos-Remus (✉)
UIECD,
Colomos 2292, Providencia,
Guadalajara Jal. 44620, Mexico
e-mail: rramos@cencar.udg.mx

K. Skeith
Department of Rheumatology, University of Alberta, Edmonton, AB, Canada

A. S. Russell · J. Homik
University of Alberta,
Edmonton, AB, Canada

R. Offer
University of British Columbia,
Vancouver, BC, Canada

J. E. Olguin-Redes
Hospital Fernando O'Caranza, ISSSTE,
Hermosillo, Sonora, Mexico

L. Sanchez
Rheumatology Department of the Hospital de Especialidades,
Centro Medico Siglo XXI, IMSS,
Mexico city, Mexico

G. Navarro-Cano
Rheumatology Department,
Universidad Autonoma de San Luis Potosí,
San Luís Potosí, México

Introduction

The age of onset in rheumatoid arthritis (RA) is recognized as one of the most important outcome predictors [1]. When

RA starts at an early age, the economic burden imposed upon a family and upon health services may be devastating. Several reports involving Caucasian patients report that the mean age of onset of RA is around 50 years [2, 3]. However, our clinical observations suggest that Mexican RA patients' disease is initiated at a younger age.

This is a proof of a concept study that explores whether the age of onset is different in Mexican and Canadian RA patients.

Patients and methods

A convenience sample of rheumatologists from Canada and Mexico were invited to participate in this exploratory proof of a concept study. The invited rheumatologists agreed to directly interview consecutive RA patients attending their clinics in a given period regarding RA disease onset. Disease onset was defined as the date patient first noticed a swollen joint. None of the participant rheumatologists were aware of the primary aim of this exploratory study at the time of this interview with their patients. Rheumatologists collected data in a worksheet designed for this proposes and sent it to a rheumatologist that did not participate with patient entries.

Statistical analysis

Differences between two continuous variables were determined using the *t* test; differences between three continuous variables were determined using one-way analysis of variance and the Scheffé test for multiple comparisons. Differences in proportions were determined using the Chi-squared test. Significance was set at $p \leq 0.05$, and the confidence intervals (CIs) are reported at 95% (95% CI).

Results

Four sites in Canada participated in the survey; referral patterns are similar among these different sites. Two sites are community-based offices and two sites are university-based rheumatology units. These four sites are localized around the same latitude (49 to 53°N). Four sites participated in Mexico; three of them are private offices seeing mainly self-referral patients, and one site is a secondary-care government hospital. The four Mexican sites are localized around the same latitude (19 to 29°N).

Table 1 shows average and dispersion measures of the RA disease onset at each site. The four Canadian sites recollected data from 130 patients; 100 (77%) were women. The reported ages of onset are consistent across Canadian sites more so when extreme values were cut (5% trimmed mean); there were no significant differences in the RA disease onset among Canadian sites (mean 95% CI for differences −10 to 16 years, $p=0.12$).

In contrast, the Mexican sites gathered data from 161 patients; 146 (91%) were women. Data are also consistent across Mexican sites, with no significant differences among the four sites (mean 95% CI for differences −6 to 10 years, $p=0.262$).

There was a significant difference between the two countries. Mexican patients began with RA almost 12 years earlier than Canadians (95% CI for difference 9 to 15 years, $p<0.001$). Distribution frequencies of RA age of onset showed that almost half of Mexicans but only a quarter of Canadians had their first swollen joint before the age of 36. In contrast, 35.5% of Canadians but only 4% of Mexicans had the onset of the disease after the age of 55 years ($p<0.001$; Table 2). Differences persisted after excluding male patients from analysis.

Discussion

Our results support the concept that RA starts at a younger age in Mexicans than in Canadians; case-ascertainment-related issues and true differences may account for this observation.

We acknowledge at this stage that case-ascertainment issues such as bias, confounding, or chance might influence the results of this study. Although the disease onset was defined in advance and participant rheumatologists are experienced clinicians that were not informed of the primary aim of the study at the time of data recollection, we may not completely rule out selection and information biases. Referral patterns may also account for the differences. Most of the Canadian RA patients are seen at least once by a rheumatologist, and almost all RA patients are referred by a general practitioner to a rheumatologist. In contrast, most of the RA patients in Mexico are not attended by a rheumatologist, and the vast majority is self-referred to a rheumatologist by word of mouth. In consequence, it is possible that rheumatologists in Mexico are attending just a subgroup of RA patients more aware about rheumatic diseases and with more resources for self-referral; these could be younger patients with better access to health-related information and possibly with different health-seeking patterns than older RA patients.

Social beliefs may act as confounders in the Mexican data; aching joints, "rheumatism," and "arthritis" are believed to be consequence of aging, so older individuals consider joint pain as a "normal" process, so they do not often consult a specialist for them [4]. We deem chance as an unlikely explanation for the results. Despite the diversity of the sites, the variability in Canadians showed no

Table 1 Rheumatoid arthritis age of onset

	Mean±SD	95% CI	5% Trimmed mean	Median
Canadian sites, *n*=patients				
1, *n*=32	48±14	43–53	48	49
2, *n*=14	44.5±14	36.5–52.5	44	43
3, *n*=59	51±16	47–55	51	54
4, *n*=25	43±16.5	36–49	42	41
Total Canadians, *n*=130	48±15.5	45–50.5	48	48
Mexican sites, *n*=patients				
1, *n*=20	40±13	34–46.2	40	37
2, *n*=71	36±11	33–38.5	36	37
3, *n*=60	35±10.5	32–37	34	34
4, *n*=10	38±8	32–44	38	37.5
Total Mexicans, *n*=161	36±11	34–38	36	36

Average and dispersion measures at each site
Differences among Canadian sites, $p=0.12$
Differences among Mexican sites, $p=0.26$
Differences between Canadian and Mexican sites, 11.7 years, 95% CI, 9 to 15 years, $p<0.001$

statistical significance, and the data were very consistent as per narrow CIs and close values between raw means and trimmed means. The diversity of Mexican sites was stronger (private vs public clinics), yet the data were even more consistent.

However, the possibility of true differences should also be considered. Latitude has been used as a surrogate to study the influence of diverse environmental variables on disease prevalence and risks across different geographic areas or throughout the world. The studied variables included solar cycle, ultraviolet radiation, geographic patterns of functional categories of human leukocyte antigen DR alleles, food characteristics, pollution, etc. [5–8]. There are some reports of the influence of latitude on the prevalence of diseases such as type 1 diabetes, multiple sclerosis, and RA [9]. For instance, a positive association of type 1 diabetes mellitus prevalence was found with increasing southern latitude of residence. For both RA and eczema/dermatitis, there were no statistically significant associations between latitude/ultraviolet radiation and disease prevalence.

Table 2 Distribution of frequencies of RA age onset by age groups in 130 Canadian and 161 Mexican patients

Age groups, years	Canadians, *n* (%)	Mexicans, *n* (%)
16–25	11 (8.5)	31 (19)
26–35	22 (17)	49 (30)
36–45	25 (19)	46 (29)
46–55	26 (20)	28 (18)
56–65	28 (21.5)	7 (4)
65 and older	18 (14)	0

Differences $p<0.001$

The diverse genetic background of the populations explored could account for our results. There seem to be differences in the RA susceptibility loci between different ethnic groups. Nowadays, it is important to consider that environmental factors modify the risk associated with genetic factors. Environmental factors are estimated to account for as much as half of the risk of developing RA [10]. Differences in social structure, lifestyle, and environment account for much larger proportions of disease than genetic differences. There seems to be a difference not explained by genetics in disease severity between RA patients of African ancestry from North America and Colombia [11, 12]. Whether the age of onset of disease was different was not considered in the report.

Cigarette smoking is so far the most plausible environmental exposure associated with seropositive RA [13, 14]. The enforcement of antismoking laws is not as strong in developing countries. This makes the potential exposure to cigarettes much more plausible from early ages than in other countries, but we were not able to record the smoking habit of the patients included.

Infectious agents have always been favorite candidates as primary causes of RA, but their precise role, if any, is still a matter of ardent debate [15]. The potential geographic variation in the exposure to diverse infectious agents should be taken into account with the results presented. Exposure to cats and budgerigars has been shown as associated with RA in a dose-dependent manner [16, 17]. We cannot exclude the possible existence of other potential animal vectors increasing this risk.

Low levels of gonadal and adrenal androgens as well as lower androgen/estrogen ratios have been proposed as predisposing conditions to initiate and maintain RA [18]. A different pattern of use of oral contraception in women in

Canada and Mexico could modify the age of onset of the disease [19], as could earlier pregnancies. In addition, pertinent to our results is the possible effect of endocrine disrupters in blocking androgen action [20]. This could predispose to a younger age of onset of the disease in countries with most severe environmental deterioration.

This is the first indication that age of onset in RA may be different in diverse geographic settings. The nature of this exploratory study does not allow us to identify causation factors. However, these results, if confirmed by further investigations, do have important implications in several areas. A younger age of onset in RA means more years of suffering in countries with a lower proportion of their national budget devoted to health. These results should also prompt further economic investigations to define if a stronger expenditure in early age, such as tumor necrosis factor blockers, could prevent decades of lost labor days in these patients. In light of these observations, we must ask the pertinent questions to find the best solutions for our future.

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