Demographic and clinical characteristics of a cohort of patients with early rheumatoid arthritis

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ABSTRACT

Introduction: Very few studies carried out with Latin American populations on the demographic and clinical characteristics of patients diagnosed with early rheumatoid arthritis (RA) can be found in the literature. **Objective:** To characterize a population of patients with early RA, prospectively followed, concerning demographic and clinical aspects and compare them with other similar cohorts. **Patients and methods:** The data presented are part of an incident cohort prospective study, in which 65 patients with early RA were evaluated and followed regularly for 36 months at the Early Rheumatoid Arthritis Outpatient Clinic of the University Hospital of Brasília (HUB, from the Portuguese). The demographic and clinical data of the initial evaluation, including general characteristics, clinical history, and physical examination were recorded. Descriptive statistics of the variables was applied. **Results:** Women (86%) with a mean age of 45.6 years, Caucasian or Black (47.6%), belonging to intermediate-low social classes (53.85%), with 8.3 years of schooling, predominated. The presenting symptoms of the majority of patients were acute (76.9%), with polyarticular onset (69.2%), persistent synovitis of the hands (90.7%), and prolonged morning stiffness (157 minutes on average). Patients had a high average score of painful (18.6) and swollen (13.9) joints and high prevalence of rheumatoid nodules (15.3%), which suggests disease with aggressive presentation in its initial phases. **Conclusion:** The demographic and clinical characteristics of patients enrolled in this Brazilian cohort differed, on several aspects, from previously published North American, European, and Latin American cohorts.

Keywords: early rheumatoid arthritis, demographic characteristics, clinical characteristics, Brazilian population.

INTRODUCTION

Despite recent developments in the management of rheumatoid arthritis (RA), the disease is still associated with potential for irreversible bone and cartilaginous damage, leading to high costs, both for the individual and society.[1]

It is known that RA has variable characteristics according to the affected population. However, most of the available information, especially regarding early RA, comes from studies carried out in Europe and the United States. Very few studies have been undertaken with Latin American populations.[2-4]

A study with a Brazilian cohort involving patients with early RA is not available in the literature. Therefore, the demographic and clinical characteristics of early RA in the Brazilian population are not known.

The objective of the present study was to characterize a prospectively followed population of patients with early RA regarding their demographic and clinical aspects and to compare them with similar Latin American, North American, and European cohorts.

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PATIENTS AND METHODS

The data presented are part of a prospective study with an incidental cohort, in which consecutive patients with a diagnosis of early RA were followed regularly for 36 months, from the time of the diagnosis on, at the Early Rheumatoid Arthritis Outpatient Clinic of the University Hospital of Brasília (HUB, from the Portuguese) of the Universidade de Brasília (UnB), Brazil.

Early RA was defined as the development of articular symptoms compatible with the disease (joint pain and edema with inflammatory pattern, associated or not with morning stiffness or other manifestations suggestive of inflammatory joint disease, according to the evaluation of a single observer) lasting more than six weeks, but less than 12 months, regardless of whether or not they met the classification criteria of the American College of Rheumatology (ACR).[5]

Demographic and clinical data from the initial evaluation were recorded, such as:

- General characteristics (age, gender, ethnic group, socioeconomic status, according to the Graffar scale,[6] and years of formal schooling).

The classification according to the ethnic group was based on the same criteria used by the study "Rheumatoid Arthritis in Latin America: a Cohort Study" – Latin-American Group for the Study of Rheumatoid Arthritis (GLADAR).[7] This classification used the information supplied by the patient about the ethnicity of his/her parents and four grandparents. Patients were questioned about their place of birth or origin of the ancestors of their parents and four grandparents and they were classified as:

c.1) Caucasians: individuals whose all four grandparents were European Caucasians.
c.2) Mixed race: individuals born in Latin America with mixture of Caucasian and Amerindian ancestors.
c.3) Afro-Latin Americans: individuals born in Latin America with at least one African ancestor, regardless of whether the other ancestors were Caucasian, Amerindians, or others.
c.4) Amerindians: individuals whose four ancestors were autochthons.

The final attribution of the ethnic group, taking into consideration the anthropomorphic characteristics of the patient, was considered a prerogative of the observer.

Categorization of the following ethnic groups was allowed: Caucasians (four Caucasian ancestors); Caucasian-black (at least one black ancestor); Caucasian-Indian (at least one Indian ancestor); Caucasian-yellow (at least one Asian ancestor); black (four black ancestors); black-Indian; black-yellow; Indian (four Amerindian ancestors); Indian-yellow; yellow (four Asian ancestors); and others.

- Data on the clinical history: clinical manifestations (duration of symptoms, type of onset of arthritis, joint involvement, persistent synovitis of the hands, duration of morning stiffness, associated manifestations);
- Data on the physical examination: general physical exam, number of articulations (28 joints), assessment of rheumatoid nodules.

Patients received the standard treatment used in our department, including traditional disease-modifying drugs (DMARDS) and/or biological response-modifying drugs, according to the patients' needs.

Descriptive analysis of the analyzed parameters was carried out.

This study was approved by the Ethics on Research Committee of the Medical School of Universidade de Brasília (CEP FM-UnB). Study registration: CEP-FM 028/2007.

RESULTS

General characteristics

Sixty-five patients with a diagnosis of early RA were initially evaluated. Mean age was 45.64 years (± 14.51), ranging from 26 to 71 years. Female gender (56 patients, 86.15%), Caucasians (31 patients, 47.69%), and the intermediate-low social class (35 individuals, 53.84%) predominated. The mean level of schooling was 8.3 years (± 4.95 years). Table I summarizes the characteristics of 65 patients analyzed in the initial evaluation.

Clinical manifestations

According to the data of their clinical history, the mean duration of articular symptoms at the time of the diagnosis was 32 weeks (± 15.4) in the cohort, of which 23 patients (35.3%) had had symptoms for less than 12 weeks – very early arthritis.

The majority of the patients had acute onset of symptoms (50 individuals, 76.02%), with polyarticular involvement (45 patients, 69.23%), and persistent synovitis of the hands (59 patients, 90.76%). The mean duration of morning stiffness was 157.53 minutes (± 108.64 minutes). On the initial physical examination, the mean number of painful articulations observed was 18.64 (± 7.02), and that of edematous articulations, 13.92 (± 4.94). Ten patients evaluated (15.38%) had rheumatoid nodules on the initial evaluation.

Table 1
Patients with early RA evaluated at HUB, according to their general characteristics (initial evaluation, n:65)

Characteristics		n (±) or n (%)
Age (years)		45.64 (± 14.51)
Gender	Male	9 (13.80%)
	Female	56 (86.15%)
Ethnic group	Caucasian	31 (47.69%)
	Caucasian/black	18 (27.69%)
	Caucasian/Indian	13 (20%)
	Caucasian/Asian	0 (0)
	Black	1 (1.53%)
	Black/Indian	2 (3.07%)
	Black/Asian	0 (0)
	Indian	0 (0)
	Indian/Asian	0 (0)
	Asian	0 (0)
	Others	0 (0)
Social class (Graffar)	I – High class	3 (4.61%)
	II – high-middle class	10 (15.38%)
	III – middle class	12 (18.46%)
	IV – intermediate-low class	35 (53.84%)
	V – low class	5 (7.69%)
Schooling (years)		8.3 (±4.95)

Parameters are presented as mean (± standard deviation) or n (%).

In the first evaluation, 42 patients (64.61%) reported fatigue; 12 (18.46%), Raynaud's phenomenon; 9 (13.84%), symptoms of sicca syndrome; and 9 (13.84%), symptoms of depression. The following were diagnosed (clinical, laboratorial, or histopathological diagnosis): anemia (12 patients, 18.46%), fibromyalgia (10 patients, 15.38%), cutaneous vasculitis (3 patients, 4.61%), episcleritis (2 patients, 3.07%), interstitial lung disease (2 patients, 3.07%), and peripheral polyneuropathy (1 patient, 1.53%). Table 2 summarizes the clinical manifestations analyzed in the initial evaluation.

DISCUSSION

Latin America has complex demographic characteristics due to its multi-ethnical origin populations, colonial heritage, and immigration patterns. The interaction of those factors resulted in a highly mixed population that varies among the different countries, with a wide variability of genetic expression.[2-4]

Data on the prevalence and incidence, as well as the characteristics of RA in Latin American populations are scarce. When analyzing the results of studies on RA undertaken in developing countries, one should not forget that disease characteristics could be affected by socioeconomic and demographic aspects and by the health system in those countries.[8]

The characteristics of the patients in our cohort were compared to the data of the GLADAR study,[7] a multinational, prospective, observational, multicenter study that evaluated 1,059 patients with early RA in 46 centers of 14 Latin American countries.[8,10] The Rheumatology Department of HUB/UnB participated in the GLADAR study with 30 patients, who were distinct from the patients included in the present study.

General characteristics

The mean age of the patients in the present study was very similar to that reported by the GLADAR (46 ± 14.2 years), but approximately five years younger than that observed in Caucasian North American and European populations.[1] This

Table 2
Patients with early RA evaluated at HUB according to clinical manifestations (initial evaluation, n: 65)

Clinical history and physical examination		n (±) ou n (%)
Duration of symptoms before the diagnosis (weeks)		32 (± 15.41)
Type of onset of the arthritis	Acute	50 (76.92%)
	Insidious	15 (23.07%)
Articular involvement	Monoarticular	3 (4.61%)
	Oligoarticular	17 (26.15%)
	Polyarticular	45 (69.23%)
Persistent synovitis of the hands		59 (90.76%)
Duration of morning stiffness (minutes)		157.53 (± 108.64)
Number of painful joints		18.64 (± 7.02)
Number of edematous joints		13.92 (± 4.94)
Rheumatoid nodules		10 (15.38%)
Other manifestations or diagnoses associated with RA	Fatigue	42 (64.61%)
	Anemia	12 (18.46%)
	Raynaud's phenomenon	6 (9.23%)
	Cutaneous vasculitis	3 (4.61%)
	Systemic vasculitis	0 (0)
	Ulcers in the lower limbs	0 (0)
	Pulmonary manifestations	2 (3.07%)
	Ocular manifestations	2 (3.07%)
	Cardiac manifestations	0 (0)
	Peripheral neuropathy	1 (1.53%)
	Fibromyalgia	10 (15.38%)
	Depression	9 (13.84%)
	Sicca syndrome	9 (13.84%)

Parameters are represented as mean (± standard deviation) or n (%).

difference could possibly be explained by demographic characteristics, which are specific to the region or by real differences in the age of symptom onset. [7]

The proportion of genders was also the same reported by the GLADAR study:[9,10] 85% of females and 15% of males (8:1), but very different than that observed in the United States and Europe, with a mean of 3:1.[1] This difference is very important, considering that gender as a predictive factor of prognosis of RA have evoked great interest in the last decades.[11] Historically, a consensus on the difference in RA presentation between men and women does not exist, but recent studies suggest that women are less prone to achieve remission with treatment.[12]

The QUEST-RA (Quantitative Standard Monitoring of Patients with RA) group, who carried out a multinational transversal study with patients with RA, evaluating 6,004 patients in 70 centers from 25 countries, including 5 centers in Brazil, concluded that disease activity (measured by the DAS-28) was more severe in women than in men. However, the authors concluded that a large part of the difference in RA presentation between genders could be due to the type of evaluation (including the use of visual analogue scales), rather than disease activity.[13]

As for the ethnic group, in our cohort Caucasians predominated, followed closely by Afro-Latin Americans, and mixed race. These data are different than those of the GLADAR study in which, following the same ethnic classification used in our study, 43% of the population were mixed race, 31% Caucasians, 19% Afro-Latin America, and 4% Amerindians.[8,9]

The ethnic composition of the present study partially reflects that of the Brazilian population, in which those that consider themselves Caucasians predominate (49.9%), followed by Brazilian mulattoes (43.2%) and blacks (6.3%).[14] However, it should be stressed the different methodologies adopted and the great difficulty to classify oneself by ethnicity in the highly mixed Brazilian population.

This difference in the ethnic composition of the population analyzed in our cohort in relation to North American and European cohorts, as well as that of other countries in Latin America,[7-9] is noteworthy, as ethnicity can influence RA evolution.[15] The social stratification of the present study was similar to that of the GLADAR study, in which 58% of the evaluated population was classified at the intermediate-low and low social classes using the Graffar scale.[8-10] The mean level of schooling of our cohort was also comparable to that reported by the GLADAR study, in which 77% of the patients referred less than 12 years of formal schooling, and 42% less than eight years.[9,10]

The information of those cohorts on socioeconomic levels and years of formal schooling are relevant, since there seems to be a relationship between these variables and RA prognosis.[16] Whether RA is more aggressive or not among patients with lower socioeconomic status is controversial, but the psychosocial effects of early RA are more severe in patients of lower social classes.[17] Bengtsson *et al*. reported the association between high socioeconomic and educational status and a lower risk for the development of RA in a population representative of the Swedish population, suggesting that environmental factors or lifestyle might influence disease evolution.[18] Pedersen *et al*. reported that the educational level was inversely associated to the risk of developing RA in the Danish population and the risk was twice as lower for those individuals with a higher number of years of formal schooling.[19]

Clinical manifestations

The mean duration of articular symptoms at the time of the diagnosis in our cohort was a little greater than that reported by the GLADAR study (6.8 ± 4.4 months),[9,10] but it is important to emphasize that more than one third of the patients evaluated in our study had had symptoms for at least 12 weeks (very initial or early arthritis).

As for the onset of symptoms, in the present study, the great majority of the patients presented acute onset of articular manifestations, differing from the results of the GLADAR cohort,[9] in which most patients presented insidious onset (68%) and addictive course (93%), and those reported by Halla *et al*.,[20] who reported acute symptom onset in 46% of the cases. The correlation between the acute or insidious onset of the symptoms and prognosis of RA is controversial.[21]

The pattern of articular involvement in our cohort was predominantly polyarticular (in approximately two thirds of the cases), and the incidence of oligo- and monoarticular involvement was higher than that reported by the GLADAR, which reported symmetrical polyarticular onset in 95% of the cases.[9] The number of articulations involved initially seems to vary among different authors: Halla *et al*.,[20] for example, reported that the predominant pattern of articular involvement was pauciarticular (44%), followed by polyarticular (35%), and monoarticular (21%). The importance of the initial pattern of involvement for the evolution of RA is controversial. Gerber *et al*.[22] reported that the initial number of articulations involved is predictive of the future functional capacity of patients with early RA. Jansen *et al*.[23] followed patients with oligo- or polyarticular early RA for six months and did not find any differences regarding the functional prognosis,

articular erosions, inflammatory parameters, or quality of life questionnaire results.

In our cohort, more than 95% of the patients complained of morning stiffness that lasted more than one hour in the first evaluation, which is longer than the duration reported by the GLADAR study (75.6%).[10] The duration of the morning stiffness is very important in early RA. Visser *et al*.,[24] in a study of consecutive patients with early RA, reported that the duration of morning stiffness was a tool to discriminate between persistent and self-limited disease, with a sensitivity and specificity of 58% and 76%, respectively. Yazici *et al*. reported that the duration of the morning stiffness reflects the functional incapacity and pain scores, showing a less marked relationship with traditional inflammation markers, such as the number of painful joints and erythrocyte sedimentation rate (ESR).[25]

It is possible that prolonged morning stiffness, observed at the initial evaluation in the majority of patients from our cohort is a marker of more active disease. However, it is important to consider the difficulty of evaluating this parameter in clinical practice, both qualitative and quantitatively.

Morning stiffness is a complex sensation, which is difficult to interpret and discriminate in relation to pain and functional limitation, as the physician or investigators' assessment is based on the patient's verbal description. Very few studies have analyzed this difficulty in the evaluation in clinical practice or investigations. Hazes *et al*. evaluated the qualitative and quantitative aspects of morning rigidity and concluded that it is not the proper tool to discriminate between RA and non-inflammatory articular disease, with a sensitivity of 74% and specificity of only 30%.[26]

Most patients evaluated in our cohort (80%) had persistent synovitis of the hands in the initial evaluation, a parameter that is related with the evolution to erosive disease.[24]

At the initial physical examination, the mean number of painful joints and inflamed joints observed in the present study was much higher than that reported by other studies. Pincus *et al*.[27] evaluated the number of painful and inflamed joints in three cohorts of RA patients: 125 patients in 1985, 138 patients in 2000, and 232 patients with early RA in 2001. The mean number of painful joints was 11, 2, and 4, and that of inflamed joints was 12, 6, and 5 in 1985, 2001, and 2001, respectively. It is possible that the greater number of painful and inflamed joints in the initial evaluation of patients in our study, when compared to other cohorts (including established RA), is a reflex of more active disease in its initial phase.

The presence of rheumatoid nodules in the initial evaluation of our cohort was 12.5%, which is higher than that reported in other cohorts of early RA, including the GLADAR (2.5%),[10] and similar to some studies of established RA.[13]

In the study of Lindqvist *et al*.,[28] the presence of rheumatoid nodules was higher than in our study. In that study, of 183 patients with early RA (symptoms for less than 24 months) followed for 10 years, 70 (38%) presented nodular disease, of which 15 (8%) developed extra-articular manifestations. A similar prevalence was reported by Corbett *et al*.[29] Those authors proposed that the elevated incidence of rheumatoid nodules in their studies could be explained by the active search (questioning and physical examination) for this manifestation during the evaluation, which could also explain the prevalence of rheumatoid nodules in our study.

Rheumatoid nodules are related with disease activity and tend to disappear with the remission of the articular involvement, and, as other extra-articular manifestations, are more common in patients with severe, polyarticular disease with positive RF.[10] The elevated prevalence of rheumatoid nodules in our cohort of early RA, especially considering that one third of the patients had had symptoms for less than 12 weeks, is another piece of information that suggests this was a population with more aggressive manifestations of the disease in its early phase.

As for other manifestations associated with rheumatoid arthritis, the development of extra-articular manifestations, Raynaud's phenomenon, and sicca syndrome was similar to that observed in other cohorts,[31] including the GLADAR study.[9,10]

It should be mentioned that fatigue was more common in our cohort (64%) than in the GLADAR study (34.9%). Fatigue is a multicausal, multidimensional and complex concept, in which several psychological, biochemical and physiological mechanisms may play a part.[32] Due to differences in definition and tools used to measure fatigue associated with RA, the prevalence rate ranges from 40% to 80%.[33,34]

The association between fatigue and RA activity lacks consensus. In some studies, evidence for the relationship among parameters related to disease activity and fatigue was observed, while in others, higher levels of fatigue are associated with symptoms of depression, pain, sleep disorders, gender and psychosocial factors.[35,36]

Data on 573 patients with RA diagnosed for less than one year (268 in Holland, 216 in Norway and 89 in France)[37] showed that fatigue measured for a period of two to three years was a determining factor of quality of life and psychosocial aspects of daily living. Another study, with 229 patients with early RA, showed the association between the elevated number of painful and inflamed joints with fatigue and depression in

the initial evaluation.[22] In the present study, the quantification of fatigue using specific measuring tools was not carried out,[38] and, therefore, we could not establish the association between fatigue and the number of affected joints.

There is no doubt about the great impact that fatigue has on the quality of life of patients with RA,[37-30] which underlies the importance of the elevated incidence of fatigue among our patients with early RA.

In our cohort, we observed symptoms of depression and/or compatible with fibromyalgia in up to 20% of the patients, which resulted in considerable reduction in quality of life, in addition to the effects on RA management..

The prevalence of depression symptoms in rheumatoid arthritis is higher than that usually observed in the general population, ranging from 13% to 47%.[40,41] This large difference is probably due to the diversity of the studied populations and the use of different questionnaires to determine the presence of symptoms of depression.[42] In the present study, the patient's affirmative response regarding the presence of sadness and lack of motivation was used as criteria for symptoms of depression.

Scott *et al*. suggested that, at least partially, pain in patients with early RA is related with depression.[43] Dickens *et al*. reported that the intensity of symptoms of depression could be attributed, at least partially, to the levels of pain experienced.[44]

Sharpe *et al*.[45] investigated this association in 22 patients with early RA and observed that pain was associated with depression, in addition to the level of disability, beliefs on the consequences of arthritis, and strategies for pain management, on the initial evaluation. Patients in the study by Sharpe developed significant worsening of depression along time. On the initial evaluation, only 15% of the patients met the criteria for "possible depression"; after 15 months of follow-up, 40% of the cases were classified as being depressed, which decreased to 35% after 21 months.

Palkonyai *et al*.,[46] following a cohort of 73 Hungarian and 45 Austrian patients with early RA reported that, except in the baseline evaluation, symptoms of depression and functional status, according to the evaluation by the HAQ, were correlated.

Regarding fibromyalgia (FM), Wolf and Michaud reported that patients with RA and FM had more severe RA when evaluated by subjective and objective parameters, with worse prognosis and quality of life, when compared to RA patients without FM.[47] Coury *et al*.[48] reported that the association between RA and FM is not a marker of worse prognosis regarding greater joint destruction (radiological evolution), but FM worsens the prognosis of RA regarding functional capacity and quality of life.

Note that the evaluation of RA activity can be complex in patients with chronic pain syndromes, such as FM.[49] Leeb *et al*.[50] compared the use of the DAS-28 (Disease Activity Score) in 62 patients with RA and in 26 patients with FM and did not observe any differences in total scores between the groups. As FM is a non-inflammatory disorder, both the ESR and the number of inflamed articulations were within normal limits and, therefore, the high DAS-28 scores were due to the global perception of health by the patient and in the elevated number of painful joints. The authors concluded that the use of DAS-28 scores to express disease activity in RA patients should be carefully evaluated in patients with coexisting FM, and such is the case of almost 29% of the patients in our cohort.

CONCLUSIONS

The demographic and clinical characteristics of the patients followed in the present study with Brazilian patients showed disagreement regarding several aspects when compared to North America, European, and Latin American cohorts, including that of the GLADAR study.

A predominance of women, with a mean age of 45 years, of Caucasian or mixed ethnicity, of intermediate-low and low social classes, with eight years of schooling, was observed.

The acute onset of the symptoms, with polyarticular involvement, persistent synovitis of the hands, and prolonged morning stiffness predominated. Patients presented a high number of painful and inflamed joints and a high prevalence of rheumatoid nodules, suggesting aggressive disease.

Differences in demographic and clinical characteristics of our cohort in relation to other studies can signal differences in serological and radiological behavior, and, possibly, in disease evolution that needs to be better evaluated in future studies.

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