The severity of rheumatoid arthritis at the first rheumatology consultation and factors associated with initial structural damage in sub Saharan patients

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Abstract

Background: The severity of Rheumatoid Arthritis (RA) at diagnosis has not been fully described in sub-Saharan Africa in recent years, nor have been the factors associated with it.
Objective: The aim of this study was to determine the frequency of severe RA at the first rheumatology consultation and assess the factors associated with this early severity.
Design: This was a retrospective study.
Methods: The study was carried out in the rheumatology service of the Yaoundé Central Hospital, Cameroon. Files (one patient = one file) of patients diagnosed with RA during January 2004-May 2018 were included. RA severity was defined by the presence of at least one of these markers: Disease Activity Score-28 with Erythrocyte Sedimentation Rate (DAS28-ESR) > 5.1, initial structural damage on hand X-rays which was defined by a Larsen score ≥ 2 per joint and the presence of Rheumatoid Factor (RF) and/or Anticitrullinated Protein Antibodies (ACPA). Files with no information to assess disease severity at the time of diagnosis were excluded. Data were analyzed with Epi-info version 7.0. Statistical significance was set at p-values less than 0.05.
Results: Forty-nine patients were included. Their mean age was 48 ± 14 years. Eighty percent of them were females. Sixty-seven percent had established RA, 33% had early-stage RA and two patients had ever smoked. None of them had received biological disease-modifying antirheumatic drugs. RA was severe in 82% of patients, with DAS28-ESR > 5.1 in 71%, positivity of at least one autoantibody found in 63% to 82%, and initial structural damage found in 55% of them. Initial structural damage was only associated with the presence of ≥ 10 swollen joint counts.
Conclusions: RA was severe from the onset in most patients and structural damage was associated with the presence of ≥ 10 swollen joint counts.

Key words: Rheumatoid arthritis, Severity, Initial presentation, Structural damage, Sub-Saharan Africa.

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune systemic disease. It affects 0.5-1% of the general population and progressively leads to irreversible joint destruction that causes disability[1]. Indeed, RA was responsible for 3.4 million disability-adjusted life years during 1990-2017[2]. Furthermore, patients with long-standing and severe RA have a shorter life expectancy of up to 10 years compared to normal subjects[3]. These high morbidity and mortality are strongly related to the severity of RA since the most severe forms are the most likely to cause (early) joint destruction[4] and are often associated with a high prevalence of comorbidities[5]. A systematic literature review including 18 studies published over a 44-year period defined severe RA from the onset as RA presenting with structural damage, autoantibody positivity, biological inflammation or high swollen joint counts[4].

In sub-Saharan Africa, RA was largely unknown until the beginning of the 21st century, resulting in long diagnostic delays in the first studies[6]. Previous hospital based studies conducted in

South, West and Central Africa have shown that RA is severe in most patients[7-13]. Given the improving awareness for RA in sub-Saharan Africa together with the ongoing reduction of severe cases of RA from the onset as recently demonstrated by the Norfolk Arthritis Register study[14], we conducted this contemporary study to determine the frequency of severe RA from the onset and assess the factors associated with initial structural damage.

Materials and methods

We carried out a cross-sectional retrospective study using files of patients (one file = one patient) aged ≥ 18 years and diagnosed with RA from January 2004 to May 2018 in the Rheumatology service of the Yaoundé Central Hospital. The diagnosis of RA was based either on the 1987 American College of Rheumatology criteria[15] or the 2010 ACR/European League Against Rheumatisms (EULAR) criteria[16] or both. Files with no information to assess severity at the time of diagnosis were excluded.

RA was considered severe from the onset if at least one of the following characteristics was found at diagnosis[4,17]; (i) disease activity score 28 with erythrocyte sedimentation rate (DAS28-ESR) > 5.1, (ii) initial structural damage on hand X-rays which was defined by a Larsen score ≥ 2 per joint[18] (iii) and the presence of Rheumatoid Factor (RF) and/or Anticitrullinated Protein Antibody (ACPA).

Bivariate analyzes were conducted to assess the factors associated with initial structural damage. Candidate factors included in the model were: number of tender joints ≥ 10, number of swollen joints ≥ 10, CRP ≥ 6 mg/l, ESR ≥ 20 mm, DAS28-ESR > 5.1, positive RF, positive ACPA and the presence of extra-articular features. The significance threshold was set at $\alpha = 0.05$. Data were entered in Microsoft excel 2013 and analyzed with Epi info version 7.0 software. Ethical clearance was granted from the Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I and administrative authorizations before data collection.

Results

Baseline characteristics of the study population: Of the 102 files retrieved, 49 were included in this analysis. Most of them were females with established RA, and two had ever smoked. Twenty-two percent of patients had extra-articular features, and 55% had radiographic erosions on extremity joints. The mean DAS28 was 5.7 ± 1.1. Eighty percent and 88% of patients respectively received methotrexate and glucocorticoids as initial treatments. None of these patients had received biological disease-modifying antirheumatic drugs. These characteristics are detailed in Table 1.

Table 1: Characteristics of the study population

Age (mean ± SD), years	48 ± 14
Females, n (%)	39 (80)
Ever smoked, n (%)	2 (4)
Diagnostic delay, median (interquartile range 25 to 75); years	36 (12-84)
Established RA*, n (%)	33 (67)
Morning stiffness > 30 minutes, n (%)	12 (24)
Hand deformations	11 (22)
Ulnar deviation, n (%)	6 (12)
Boutonniere deformity, n (%)	6 (12)
Z-deformity, n (%)	3(6)
Camel back deformity, n (%)	2 (4)
Swan neck deformity, n (%)	1 (2)
DAS28-ESR	5.7 ± 1.1
NSAIDs, n (%)	37 (75)
Glucocorticoids, n (%)	43 (88)
Methotrexate, n (%)	39 (80)
Hydroxychloroquine, n (%)	9 (18)
Sulfasalazine, n (%)	2 (4)

Established RA* established rheumatoid arthritis: duration ≥ 2 years; DAS28-ESR = disease activity score-28 with erythrocyte sedimentation rate; NSAIDs = non-steroidal anti-inflammatory drugs

Frequency of the severity of RA: According to the predefined criteria, RA was severe in 40 (82%) patients. Thirty-five (71%) had high disease activity, 40 (82%) had positive RF, 31 (63%) had positive ACPA and 27 (55%) had initial structural damage. The frequency of markers of severity is depicted in Table 2.

Table 2: Frequency of markers of RA severity

Clinical	No. (%)
Increased number of tender joints (> 10), n (%)	27 (55)
Increased number of swollen joints (> 10), n (%)	11 (22)
Extra-articular features, n (%)	11 (22)
Fever, n (%)	9 (18)
Weight loss, n (%)	9 (18)
Anaemia, n (%)	5 (10)
Sicca syndrome, n (%)	3 (6)
Subcutaneous nodules, n (%)	2 (4)
Pulmonary fibrosis, n (%)	1 (2)
Pericarditis, n (%)	1 (2)
Fatigue, n (%)	1 (2)
Biological	
Increased ESR (>20 mm), n (%)	43 (88)
Increased CRP (> 6 mg/l), n (%)	41 (84)
RF positivity, n (%)	40 (82)
ACPA positivity, n (%)	31 (63)
Radiographic	
Larsen score per joint ≥ 2	27 (55)
Disease activity	
DAS28-ESR> 5.1	35 (71)

Factors associated with initial structural damage: Initial structural damage was associated to the presence of more than 10 swollen joints: odds ratio 18 (95% confidence interval: 1.05-506.06), p-value = 0.04.

Table 3: Bivariate analysis of factors associated with initial structural damage

Variables	OR (95% CI)	P-value
Number of tender joints > 10	4.67 (0.41-130.66)	0.23
Number of swollen joints > 10	18 (1.05-506.06)	0.04
Extra-articular features	3.67 (0.26-45.16)	0.3
CRP ≥ 6 mg/l	0.33 (0.01-16.14)	0.49
ESR ≥ 20 mm	-	0.51
Positive RF	-	0.07
Positive ACPA	0.94 (0.1-10.34)	0.68
DAS28-ESR > 5.1	0.67 (0.07-7.68)	0.56

Discussion

In this study, we found that 82% of patients had severe RA at the onset; i.e. 71% with high disease activity, 63 to 82% with positivity of at least one autoantibody, and 55% with initial structural damage. Initial structural damage was associated with only the presence of ≥ 10 swollen joint counts.

The results of this study are in concert with data from Mathieu and colleagues' systematic review[4], which found a high prevalence of markers of RA severity in 18 studies published from 1998 to 2009 and including European and American patients. These results are also consistent with previous studies that found a high frequency of markers of severity at the time of diagnosis of RA in African patients with some differences in proportion[9-13], probably as a simple reflect of differences in sample sizes and methods for calculation of the DAS28. Furthermore, the prevalence of autoantibodies is even more difficult to compare between studies in sub-Saharan Africa because detection methods vary from one study to another[9-13]. The prevalence of structural damage found in this study is however comparable to those described in Senegal[13] and Democratic Republic of the Congo[10], although those studies assessed structural damage using the score of van der Heijde unlike here where the score of Larsen was rather used.

This high frequency of markers of early RA severity is likely to be underpinned by genetic and environmental factors[19]. Among the genetic factors, the shared epitope of HLA-DRB1 is the one that has already been identified in sub-Saharan African patients[9,10]. In fact, it has been associated with a high production of autoantibodies in both sub-Saharan Africans and Caucasians[9]. The high production of autoantibodies would promote a high level of inflammation, severe disease activity, and therefore significant structural damage. Inflammation would promote structural damage during RA through the action of pro-inflammatory cytokines such as tumour necrosis factor alpha which activates osteoclasts, thus promoting osteolysis[20]. However, the shared epitope is probably not the main determinant of this severity, since it is absent in the majority of sub-Saharan African patients, despite prevalence rates of autoantibodies comparable to those in Caucasians[9,10]. The effect of other non-HLA genes such as PTPN22[19] should therefore be explored locally. Among environmental factors, tobacco does not appear to contribute significantly to the (early) severity of RA in sub-Saharan Africa. Indeed, smoking is only documented in a minority of patients in most series as in this study[9,10,12]. Since most sub-Saharan African women have lifetime exposure to wood smoke, household air pollution is an environmental factor that should be specifically investigated with respect to RA in sub-Saharan Africa[21]. The long diagnostic delay due to a low index of suspicion and late referral to rheumatology would also contribute to this high frequency of early RA severity[9,13]. Of note, there has been a gradual decrease in RA activity over time in the United Kingdom as a result of increasing early referral of patients to rheumatologists[14].

These results are relevant in several ways for national and regional rheumatologists as well as local stakeholders. In particular, strategies aimed at early detection and management of RA should be part of chronic non-communicable disease programs already existing in most sub-Saharan African countries. These strategies could involve the local implementation of World arthritis day (12th October), during which sensitization campaigns targeting the general public and non-rheumatologists health professionals could be organized. Extension of rheumatology training programs across countries and strengthening of RA lectures in medical students' curricula could further help to improve RA diagnosis within the region. Diagnosed and treated patients need to be followed up more closely. A support from international arthritis funding bodies is also warranted to improve the availability and affordability of effective biological Disease-Modifying Antirheumatic Drugs (bDMARDs), as this study suggests that a high proportion patients need to be started on bDMARDs within three months of diagnosis[4].

The small sample size of this study precludes strong conclusions. Information bias related to the retrospective nature of the study did not allow us to specify all the pertinent markers of RA severity (e.g. health assessment questionnaire), or to stratify RA severity with respect to disease duration. We hope this study will foster future relevant high-quality research accounting for the above mentioned shortcomings.

Conclusions

Most patients presented with early severe RA, and structural damage was associated with a high number of swollen joint counts. These findings should be confirmed in future local large prospective studies.

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Ethics approval and consent to participate

The Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I approved the study. Informed consent was not requested as this was a retrospective study. We have respected the terms of the Helsinki Declaration.

Consent for publication

All authors consented to publish the manuscript in African Journal of Rheumatology.

Competing interests

We declare that we have no competing interests.

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