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ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS IN WESTERN ALGERIA: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Introduction: *Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease of multifactorial origin in adults and chronic autoimmune disease with a prevalence of 0.5% in the world. The aim of this study was to determine the clinical characteristics, therapeutic parameters and estimating the impact of smoking on disease onset of RA characteristics in Western Algerian region (Sidi bel Abbes area in particular).*

Methods: *A retrospective study was carried out on medical records of 300 patients with RA diagnosed (between 2015-2019) in the internal medicine department of the University Hospital of Sidi Bel Abbes region.*

Results: *Out of all the enrolled participants in this study, 257 (85.7 %) were females and 43(14.3%) were males. The mean age at diagnosis was 52.71±12.22, ranging from 14 to 84 years old. The average time of disease duration was 4.17±3.93 years. moderate activity was noted in 53.7% of subjects. The main medical histories were high blood pressure (41%), type 2 diabetes (84.7%), hypothyroiditis (6 %) and osteoporosis (4.7%). The majority of patients (81.3%) were seropositive and used DAMRDS (Disease Modifying Anti-Rheumatic Drug) as treatment. Moreover, evidence of association between smoking and ACPA was noticed with p=0.001, and most of the smokers were hypertensive (p =* ***0.0001)*** *and suffered from Hashimoto's thyroiditis (****p<0.0001).***

Conclusion: *This study showed that relatively older adults were commonly affected; the majority were seropositive and diagnosed in moderate stage of the disease. Smoking increased the risk of ACPA(anti-citrullinated protein antibodies) secretion and the emergence of comorbid diseases.*

Keywords: *Rheumatoid Arthritis Patients; Clinical Characteristics; Treatment; Smoking; Western Algeria Region.*

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease in adults(1). It is characterized by bilateral and symmetrical synovitis of appendicular skeleton joints and upper cervical spine. It affects very little the antheses, unlike spondyloarthritis, and it usually starts at the hand, wrist and forefoot(2). It is considered as an autoimmune disease because of the presence of rheumatoid factors (RF) and Anti Citrullinated Peptides Antibodies (ACPA) (3). Clinical and biological features of the disease vary according to the geographical location which could be explained by life style and cultural differences(4). The prevalence of RA is 0.5% worldwide and it varies from country to country (5). However the pathology is mostly common among the age groups of 35 to 55 years, and it is four times more frequent in women than men(6).

In Algeria the number of rheumatologists is modest compared to African countries. However, the difficulty of access to biological treatment is a main problem due to their availability only at university hospitals (4). Moreover, the major survey conducted in Algeria from February 14th to April 11th, 2013, identified over 100,000 cases of Rheumatoid arthritis RA (7).

The associations of smoking and genetic factors were incriminated in the development and the severity of RA (8–11). Interestingly, previous studies have underlined the impact of smoking on RA outcomes such as disease activity, radiologic damages, positive ACPA(8)

Thus, the aim of this study was to describe clinical characteristics of patients with rheumatoid arthritis in the Western Algerian region and the impact of smoking on RA outcomes.

PATIENTS AND METHODS

Population

This hospital-based study was carried out at the internal medicine department of the University Hospital of Sidi-bel- Abbes region from January 2015 to April 2019.

We carried out a retrospective epidemiological study using records of 300 patients' with RA diagnosed according to the ACR 1987 criteria. The following variables were considered as factors: age at onset, gender, disease duration, joint disorders, DAS28 (Disease activity score 28), comorbidities, biological assessment, treatments, and smoking at disease onset.

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A comparative study between smokers and non-smokers RA patients was performed.
Concerning DAS28, the threshold values are less than 2.6 for remission, from 2.6 to 3.2 for low activity, between 3.2 and 5 for moderate activity and over 5 for high activity(8).

The statistical analysis
Regarding the statistical analysis, the result was presented as frequencies with percentage and mean with standard deviation (SD). For comparison, continuous variables were tested using the independent sample t-test and Pearson chi-square test ($\chi 2$) was used for categorical variables. The level of significance was at p-vale <5%. All data were processed and analyzed using SPSS 22.0 (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. August 2013).

Ethics: The Medical Committee of Sidi bel Abbes University Hospital and Department of Biology, Djillali Liabes University approved the study.

RESULTS

Demographic, clinical characteristics and medication related information
Three hundred (300) cases were enrolled in this study between 2015-2019 with 257 (85.7 %) females and 43 (14.3%) males). A clear female predominance was noticed with the female to male ratio of 5.95, median age of the enrolled participants was 52.71±12.22, ranging from 14 to 84 years old. The most affected age group was the 56-60 years (19.7%).

More cases were from urban areas (72.7%) than rural area (27.3%). The average disease duration was 4.17±3.93.

The most reported joint disorders were on hands (68.3%) followed by wrists (62.3%), knees (55.7%), elbows (37.3%), shoulders (35%),feet (31%), and ankle (14.7%). 15.7% of patients had erosive rheumatoid arthritis.

After the classification according to the disease activity score 28 (DAS28), we noticed a predominance of moderate activity (53.7%), followed by high disease activity (32.3%), low activity (13%), and finally remission (1%).

The inflammatory and biological assessment showed that 198 (66%) of patients had a positive CRP (C reactive protein), 247(82.3%) had an accelerated Erythrocyte Sedimentation Rate (ESR) and 64(23.1%) had anemia.

Among the included patients, 244(81.3%) were seropositive for RF(Rheumatoid Factors) and 242 (80.7%) were seropositive for ACPA. Only 5.7% were demonstrated infected with Escherichia coli (Table 1).

The most recorded medical histories were: menopause (45.5% of females) followed by high blood pressure (41%), type 2 diabetes (15.3%), Hypothyroiditis (6%), and osteoporosis (4.7%) (Table 2).

Leflunomide was the most commonly used DMARD followed by Methotrexate, *Glucocorticoid*, non-steroidal anti-inflammatory drugs, Sulfasalazine and Hydroxychloroquine. 80 (26.7%) of patients were treated by biotherapy, the most used was tocilizumab (11.3%) (Table 3).

Smoking Status:
According to the findings, 9% were smokers (P<0.0001).Smokers did not differ in age, radiologic progression and DAS28 comparing to non -smoker patients. However, a significant relation was found between smoker group and ACPA titer (p=0.001) but not with RF and ESR(Table 4).
With regards to comorbidities, the study revealed that, majority of smokers suffered from high blood pressure (p = **0.0001)** and Hashimoto's thyroiditis **(p<0.0001).** Moreover**,** 3 smokers patients suffered from Pulmonary fibrosis (**P=0.0001**) (Table 5).

Table 5: The comorbidities profile of RA smoking patients

Comorbidities	Smoker	Non-Smoker	Pvalue *
high blood pressure	21(7%)	102 (34%)	0.0001
Type 2 diabetes	2(0.7%)	44 (14.7%)	0.231
Hashimoto's thyroiditis	13 (4.3%)	5(1.7%)	<0.0001
Crohn disease	0	4(1.3%)	0.527
osteporosis	0	14(4.7%)	0.228
Pulmonary fibrosis	3(1%)	1(0.3%)	0.0001
Scleroderma	0	5(1.7%)	0.478
gastric ulcer	0	3(1%)	0.584
vitiligo	0	3(1%)	0.584
Anemia	4(1.3%)	60(20%)	0.386

* Pearson chi-square test ($\chi 2$)

Table 1: Characteristics of the RA patients

Characteristics	Rheumatoid arthritis n=300
Mean disease duration in years	4.17±3.93
Sex	
Female	257(85.7%)
Male	43(14.3%)
Age Years	52.71±12.22
14-30	14(4.7%)
31-36	19(6.3%)
37-42	29(9.7%)
43-48	39(13%)
49-54	54(18%)
55-60	59(19.7%)
61-66	52(17.3%)
67-72	27(9%)
73-78	5(1.7%)
79-84	2(0.7%)
Area of residence	
Rural	82(27.3%)
Urbain	218(72.7%)
The seat of joint damage	
Hands	205(68.3%)
Wrists	187(62.3%)
Knees	167(55.7%)
Elbows	112(37.3%)
Shoulders	105(35%)
Feets	93(31%)
Ankle	44(14.7%)
Erosion	47(15.7%)
Disease activity	
Remission	3(1%)
Low	39(13%)
Moderate	161(53.7%)
Hight	97(32.3%)
Anemia	64(21.3%)
Leukocytosis	21(7%)
Thrombocytosis	5(1.7%)
Leukopenia	9(3%)
Mean CRP titer (mg/l)	18.40±28.66
Positive CRP	198(66%)
Mean ESR titer (mm/h)	43.70±24.80
Accerelated ESR	247(82.3%)
Mean Rheumatoide factor titer (UI/ml)	70.40±75.73
Positive RF	244(81.3%)
Mean ACPA Titer (UI/ml)	195.49±167.09
Positive ACPA	242(80.7%)
Cytobacteriological examination of urine	
Escherichia coli	17(5.7%)

DAS28: disease activity score 28, CRP: C- reactive protein; ESR: Erythrocyte Sedimentation Rate RF: Rheumatoid Factors; ACPA : Anti Citrullinated Peptides Antibodies.Values are expressed as number (percentage) or mean ± standard deviation

Table 2 : The comorbidities profile of RA

Medical history	Number (%)
Menopause	117(45.5%)
high blood pressure	123(41%)
Type 2 diabetes	46(15.3%)
Hashimoto's thyroiditis	18(6%)
Crohn disease	4(1.3%)
Scleroderma	5(1.7%)
Sjogren	2(0.7%)
Psoriasis	1(0.3%)
osteopenia	4(1.3%)
osteporosis	14(4.7%)
Pulmonary fibrosis	4(1.3%)
Asthma	4(1.3%)
Tuberculosis	2(0.7%)
gastric ulcer	3(1%)
vitiligo	3(1%)
Tobbaco	27(9%)

Table 3: Medications RA Patients

Treatment	Number (%)
Leflunomide (Arava)	252(84%)
Methotrexate	244(81.3%)
Glucocorti-coid (Precortyl)	164(54.7%)
No Steroidal Anti-Inflammatory	112(37.3%)
Salazopyrine	14(4.7%)
Hydroxychloroquine (Plaquenil)	5(1.7%)
Glibil	4(1.3%)
Biotherapy	34(11.3%)
Tocilizumab	22(7.3%)
Adalimumab	9(3%)
infliximab	9(3%)
Etanercept	9(3%)
Rituximab	6(2%)

Table 4: Characteristics of RA smoking patients

	Smoker	Non- Smoker	P value
Age	52.96±12.70	52.69±12.20	0.91[1]
Gender			
Female	0	257(85.7%)	<0.0001[2]
Male	27(9%)	16(5.3%)	
Erosion	8(2.7%)	66(22%)	0.53[2]
DAS28	4.58±1.08	4.53±1.22	0.83[1]
The seat of joint damage			
Hands	18(6%)	186(62%)	0.87[2]
Wrists	18(6%)	169(56.3%)	0.62[2]
Knees	16(5.3%)	151(50.3%)	0.96[2]
Elbows	12(4%)	100(33.3%)	0.42[2]
Shoulders	8(2.7%)	96(32%)	0.56[2]
Feets	9(3%)	84(28%)	0.78[2]
Ankle	6(2%)	38(12.7%)	0.24[2]
CRP	14.42±12.73	18.79±29.76	0.45[1]
ESR	41.48±25.63	43.92±24.75	0.62[1]
RF titer	79.13±50.56	69.53±77.79	0.53[1]
ACPA titer	296.04±159.95	185.55±164.74	0.001[1]

1 : the independent sample t- test

2: Pearson chi-square test ($\chi 2$)

DISCUSSION

To the best of our knowledge, the current study was the first one of its kind that studied the profile of rheumatoid arthritis in western Algeria in general and Sidi bel abbes region in particular, over a period of 4 years (2015-2019). This study aimed to describe the clinic-demographic profile of Rheumatoid Arthritis patients in western Algeria and examined the correlation between RA characteristics and smoking.

Rheumatoid arthritis is an autoimmune disease characterized by a feminine predominance (9,10), which is in agreement with our findings with a sex-ratio of 5.796 (female to male).

The mean age of patients at disease onset was 52,717±12,2273, and the most affected age group in our study was 56-60 years (19.7%). These data are comparable with those found by Slimani et al(4), who noticed that the most common age group was 41 and 60 years old with an average age of 50.10± 14.50. Moreover, the series of Machado-Alba et al(11), noted an average age of 53.2±13.9.

A sequence of joint damage was observed in the Andia et al series(12) in which these attacks started at the hand's (47.5%), followed by the wrist (18%), shoulders (11%), elbow (9.5%), ankle (6.5%), foot (5%) and knees (2%). Other study series of Ferreyra et al (13) showed different frequency of same joint damage. These results are comparable with those found in our series which showed a high frequency starting with hands followed by wrists, knees, elbows, shoulders, feet, and ankle.

The mean DAS28 (4.54±1.21) was very close to those reported in the series of Gülfe et al , Slimani et al at (4.3±1.4) (4,14), but different from other reports due to a late referral system (15,16).

CRP(C-Reactive Protein) seems to be the best test for measuring the acute phase of RA(17–19). Our study results indicated that 66% of patients had a positive CRP, which is in agreement with the findings of Humphreys et al (20) who showed that 48% of patients had a positive CRP. Brunier et al finding is also similar to our findings(21).

The combination of the two CRP and ESR biological tests provides information for a better diagnosis (21). The mean ESR was comparable with studies from Egypt (22) and Morocco (23).

RF and ACPA are important markers for the diagnosis of rheumatoid arthritis(24). Brunier et al (21) reported that 76.5% of patients had a positive RF and 66.7% had a positive ACPA, and 78.5 % had a positive RF.

In the survey of Ouali et al, 79.7% had a positive ACPA (25). Tantayakom et al revealed the presence of RF and ACPA among 70.4 and 72.4% patients respectively (15). According to our results, positive RF and ACPA was found in 81.3% and 80.7% of cases respectively.

56.8% of patients were postmenopausal in the findings of Lehlou et al (26). Similarly, the series of Ajlani et al(27) noted that 56.25% of women were menopausal. These results are comparable to our findings with a rate of 45.5%. This could be due to the decline in ovarian function (28,29).

Regarding comorbidities, the presence of hypertension in RA patients is reported to be significantly increased due to the oxidative stress (30). On the other hand insulin resistance was associated with increased levels of inflammatory mediators (interleukin 6; TNFα) in RA which explain the relationship between Type 2 diabetes and RA(31). Dougados et al (32) found that 40% of patients had hypertension, and 25% had type 2 diabetes (33). Jeong et al reported that 30.3% of cases had hypertension and 12.9% were diabetic. Our data indeed confirmed these results.

Many investigations showed the association between RA and osteoporosis mainly in premenopausal stage (34–36). According to our findings, 4.7% of patients suffered from osteoporosis. Furthermore, we found that 6.0% had Hypothyroiditis, scleroderma (1.7%), Crohn's disease (1.3%), Sjögren's syndrome (0.7%) and psoriasis (0.3%). These findings are also comparable with those of Machado et al (11) who showed that 10.2% of patients had other autoimmune diseases.

Methotrexate (MTX) and luflodamine were the most used treatments for RA (10). Similarly, Tantayakom et al (15) noted that MTX was prescribed in 88.4% of cases. Additionally, Machado-Alba et al (11) ensured the predominance of the MTX and luflodamine prescription. The current study also identified that, luflodamine (84.0%) and MTX (81.3%) were the most widely used classical background therapy.

Biotherapies are now part of therapeutic arsenal chronic inflammatory rheumatism such as rheumatoid arthritis (37). They differ from general public hospital to private hospital which explain the difficulty to access biological treatment (38). Slimani et al (4) stated that 4% of patients were treated with biotherapy and about 20% of patients were treated with biotherapy in the Machado-Alba et al series(11). With the current study, 26% had received a biotherapy.

Regarding the correlation of smoking status with some socio-demographic and clinical profile of RA patients, smoking was only associated with sex where more males smoke than females (P<0.0001). Similarly findings from the SCQM-RA registry in Switzerland reported that smokers were more often males. However, there are also other findings showing women as more smokers comparing to males(39,40). This is in contrast to our results.

Our findings demonstrated no difference in radiologic damages, disease activity, between smokers and non-smokers. These results are similar to Ruiz-Esquide et al, Finckh et al findings (39,41). But not replicated in other finding(42,43), which could be explained by the difference in the type of statistical analysis processed.

The increase risk of RA development and ACPA secretion were demonstrated associated with HLA-DRB1 genotype and smoking.
(44,45). Accordingly, a significant association between smoking and ACPA was observed (p=0.001) in the present study.

Smoking can have an impact on the development of associated comorbidities (46,47). Effectively, we noticed a significantly increased risk of Hyepretention, Hashimoto's thyroiditis, and pulmonary fibrosis among smoker group. Our results in line with several research studies; nevertheless, we worked over providing valuable information in order to establish the clinical, therapeutic features of the RA and the impact of smoking at disease onset in Western Algerian population. Besides, this study had several limitations; among which patients were evaluated according to AC R 1987 inclusion criteria.

In addition, the study is based on a single center with a small simple size, the lack of structural and functional quality assessment (SQA) of all patients, the insufficient information on average number of cigarettes smoked per day, duration of smoking, the lack of genetic testing in patients' files because of their cost.

Conclusion

In general, RA affected commonly older adults. The main reported joint disorders were on hands followed by wrists. Most of patients were seropositive and presented with moderate activity. Luflodamine and Methotrexate were the most commonly used treatments. Fewer patients were received biological treatment. Smoking at disease onset was associated with male gender, ACPA secretion and associated comorbidities such as hypertention and Hashimoto's thyroiditis.

For a better management of rheumatoid arthritis, more research on the impact of smoking on RA onset and severity are needed .

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