Rheumatoid arthritis: A single-center Egyptian experience


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Rheumatoid arthritis: A single-center Egyptian experience


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ABSTRACT

Objective: Demonstration of rheumatoid arthritis (RA) characteristics in a large cohort of Egyptian patients.

Methods: Retrospective analysis of data of 3219 RA patients attending the Rheumatology outpatient clinic, Kasr Alainy Hospital, Cairo University; from January 1995 till December 2015.

Results: Mean age at disease onset was 36.1 ±13.4 years; 2774 (84%) were females and mean disease duration was 12.9 ±7.9 years. Regarding number of joint affected at disease onset; polyarticular pattern was found in 77.1%, pattern of joint involvement; combined small and large joints involvement was in 83.2%, subcutaneous nodules in 14.2%, interstitial lung disease in 0.3%, secondary Sjogren’s syndrome in 10.5%, hand bony erosions at diagnosis in 20.6%. Rheumatoid factor was positive in 52%. There was annual increase in the newly diagnosed cases (P = 0.017) reflecting increase in patients’ awareness and improvement of medical service, also annual increase in: mean age of onset (P < 0.001) reflecting changes in health measures, also in cases with monoarticular or oligoarticular patterns at disease onset (P = 0.02, 0.01 respectively) reflecting earlier diagnosis of patients and in patients with small joint involvement (P = 0.001) with a significant decline in: polyarticular pattern (P = 0.001), combined small and large joint affection (P < 0.001), and number of cases with hand bony erosions (P = 0.01) denoting earlier diagnosis, tight disease control.

Conclusion: We found a female predominance, younger age at disease onset, lower frequency of extra articular manifestations, more frequent polyarticular pattern at disease onset and less erosive disease, denoting changing referral patterns, earlier diagnosis, improved disease control in Egyptian RA patients over 2 decades.

Abbreviations: SNs: Subcutaneous nodules; 2ry SS: 2ry Sjogren’s syndrome; ILD: Interstitial lung disease; ACPA: Anti-cyclic citrullinated peptide antibodies; DMARDs: Disease modifying anti-rheumatic drugs.

KEYWORDS

Egypt; epidemiology; rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a common autoimmune systemic inflammatory disease with an overall prevalence of 0.5%-1% (Aletaha et al., 2010). The interaction of
genetic and environmental factors result in a cascade of immune reactions (Aletaha et al., 2010). A number of extra-articular manifestations and comorbidities are present in RA patients, which result in increased mortality (Gibofsky, 2014). RA is seen more often in females with an overall female to male ratio of 2:3 (Doran et al., 2002).

Many risk factors are associated with an increased risk of RA, ranging from infections and vaccinations to hormonal risk factors, such as breastfeeding and number of pregnancies, as well as lifestyle-related factors, such as diet, smoking, and obesity. In addition, studies have suggested an association between RA and periodontitis (Gerlag et al., 2016).

Previous studies suggested that RA patients of different ethnic origins may exhibit different manifestations and outcomes, which enables the development of different targeted treatment modalities (Almeida Mdo et al., 2014). In our country, there are few reports about disease manifestations and characteristics of RA especially among large Egyptian cohort along a long term period of follow up; the present study was designed to describe the demographic, clinical characteristics of patients with RA attending a tertiary Egyptian medical institute over a period of 20 years.

Material and methods

Study design

This was a retrospective, observational, single center, Egyptian study.

Data source

The data source for the current study was the registration follow-up files of a cohort of 3219 RA patients aged ≥18 years who fulfilled the 1987 ACR revised criteria for diagnosis of RA (Arnett et al., 1988), attending the outpatient clinic of Rheumatology Department in Kasr Alainy Hospital, Cairo University from 1995 to 2015. This tertiary medical center receives around 20,000 case/year with different rheumatic diseases (14,000 case/year as new cases and 6000 case/year as follow-up patients). The protocol was reviewed and approved by the Research Ethics Committee (REC) (ethics approval number N-27–2017). We did not rely on the new 2010 ACR/EULAR criteria because the studied RA Egyptian patients were diagnosed from 1995 and we wanted to compare them with RA cases from previous studies which also relied on the older criteria.

Data collection

Demographic characteristics included: {age at disease onset and age at initial visit which is the age of diagnosis, sex, residence, marital status, consanguinity, family history of autoimmune disease, and whether smoker or not}.

Clinical data included: {disease duration, number of joints affected; in the form of polyarticular, oligoarticular, or monoarticular at disease onset, types of joint involvement at disease onset as small, large joints, or combined small and large joints}
- Presence of extra-articular manifestations (e.g., subcutaneous nodules (SNs), 2ry Sjogren’s syndrome (2ry SS), skin vasculitis and interstitial lung disease (ILD) were also documented)
- Serological tests as rheumatoid factor (qualitative rheumatoid factor) and anti-cyclic citrullinated peptide antibodies (ACPA) were included.
- Plain radiographs of hands and wrists were assessed for the presence or absence of bony erosions.
- History of drug intake was also reported {disease modifying anti-rheumatic drugs (DMARDs); methotrexate, leflunomide, antimalarial drugs, and gold therapy and glucocorticoids.
- History of comorbidities, e.g., hypertension, diabetes.

**Procedures to improve case finding**

In order to minimize selection bias, patients who missed regular monthly follow up for more than 5 years were excluded from the study.

**Statistical methods**

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) version 21. Numerical data were summarized using means and standard deviations. Categorical data were summarized as frequency and percentages. Time trend analysis was done using linear regression model. All P values are two-sided; P value ≤ 0.05 were considered significant.

**Results**

**Demographic characteristics**

A total of 3219 RA patients were identified in a 20 years’ interval (1995–2015). Their mean age at disease onset ranged from 18 to 61 with a mean of 36.1 ± 13.4 years. Disease duration ranged from 0.5 to 53 years with mean of 12.9 ± 7.9 years. Around 24.9% of patients with subcutaneous nodules were smokers while only 16.4% were nonsmokers (P = 0.001), moreover 34.5% of patients having hand erosions at diagnosis were smokers vs 30.5% nonsmokers (P = 0.225), also RF was positive in 66.9% of smokers and negative in 64% (P = 0.369). Demographic data of our patients are shown in Table 1, while Table 2 describes their disease characteristics.

**Drug intake by the studied RA population**

Methotrexate was received by 2668 (82.8%) patients, hydroxyl chloroquine by 1641(51%), leflunomide by 606 (18.8%), Gold therapy by 551.7%), and glucocorticoids by1452 (45%) patients. None of the patients were using biological therapy.
Variations in RA characteristics during the past 20 years

There was a significant statistical annual increase by 0.13% in the newly diagnosed cases (P = 0.017) throughout the studied period (Figure 1), while there was a significant annual decrement by 0.4% in female % (P = 0.02). Also, we found a significant annual increase in the mean age of disease onset by 0.2 year (P < 0.001) (Figure 2).

Concerning the number of joint affection at RA onset in our patients; there was a statistically significant annual increase in monoarticular and oligoarticular presentations at disease onset by 0.1% and 0.9% (P = 0.02, 0.01 respectively). On the contrary, polyarticular pattern showed significant annual decline by 1.2% (P = 0.001) (Figure 3).

Regarding types of joints affected at disease onset, there was an annual decrement in combined small and large joint affection by 0.9% (P < 0.001), while small joint affection showed a steady annual increment by 0.6% (P = 0.001) (Figure 4).

Table 1. Demographic data of the studied RA population.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Frequency (N (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial visit, diagnosis (years) Mean± SD</td>
<td>20–75 (40.5 ± 12.6)</td>
</tr>
<tr>
<td>Sex (Females)</td>
<td>2774 (84%)</td>
</tr>
<tr>
<td>Residency</td>
<td></td>
</tr>
<tr>
<td>Great Cairo</td>
<td>2179 (67.8%)</td>
</tr>
<tr>
<td>Delta, Lower Egypt</td>
<td>146 (4.5%)</td>
</tr>
<tr>
<td>Upper Egypt</td>
<td>241 (7.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>653 (20.2%)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>163 (5%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>303 (9.4%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>346 (10.7%)</td>
</tr>
<tr>
<td>Married</td>
<td>2624 (81.6%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>43 (1.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>84 (2.6%)</td>
</tr>
<tr>
<td>Widow</td>
<td>122 (3.8%)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>91 (2.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>266 (8.2%)</td>
</tr>
<tr>
<td>Positive family history of autoimmune diseases</td>
<td>243 (7.5%)</td>
</tr>
</tbody>
</table>

Figure 1. Variations in newly diagnosed RA patients.

Variations in RA characteristics during the past 20 years

Table 1. Demographic data of the studied RA population.
Figure 2. Variations in sex distribution of RA patients.

Figure 3. Variations in pattern of joint involvement.

Figure 4. Variations in type of joint involvement.
Presence of 2ry Sjogren’s syndrome increased annually by 0.5% (P = 0.03), while subcutaneous nodules decreased annually by 0.4% (P = 0.068).

Annual decline in the number of cases with bony hand erosions at diagnosis by 0.5% was detected (P = 0.01). Females were more prone to have erosions (33% versus 29% in males); although this was not statistically significant (P = 0.39). Also, RF positive cases were significantly higher in the erosive group (34% versus 28% seronegative) (P = 0.019).

Discussion

To the best of our knowledge, this is the first and largest retrospective study describing demographic and disease characteristics of RA among a large cohort of Egyptian patients over a long period of time (20 years).

Our results showed a higher incidence of RA in women (5.2:1), this was comparable to that reported in Western population (4–5:1) (Kvien et al., 2006) and in Algeria (5.9:1) (Slimani et al., 2014) but was lower than reported in the Brazilian population (8:1) (Almeida Mdo et al., 2014).

Females represented 84% of the sample size matching with that observed in the COMORA (COMOrbidities in Rheumatoid Arthritis) study (81.7%) conducted on 4586 RA patients from 17 different countries (Dougados et al., 2014), also in agreement with a study conducted by Alian et al, 2017 on 1142 RA Egyptian patients (Monocentric study) where females represented (79.6%) of cases (Alian et al., 2017).

The mean age of our RA patients at disease onset was 36.1 ±13.4 years and at initial visit where it was diagnosed was 40.5 ±12.6 years which was comparable to that mentioned by Imanaka et al (Imanaka et al., 1997) where it was (37.5 ±14.1 and 42.6 ±14.3, respectively). While it was lower than that reported in other populations, e.g., Omani RA patients (44.5 ±14.5 ys) (Al-Temimi, 2010), Algerian (50.1 ±14.5 ys) (Slimani et al., 2014), Brazilian (47.5 ±11.03 ys) (Almeida Mdo et al., 2014), and that reported in the COMORA study (56 ±13 ys) (Dougados et al., 2014).

The mean age of our RA patients at disease onset was 36.1 ±13.4 years and at initial visit where it was diagnosed was 40.5 ±12.6 years, showing that there was time delay between age of onset and diagnosis which may be attributed to the fact that patients sought medical advice from primary care physicians or other specialists such as orthopedic surgeons, rather than consulting a rheumatologist from the outset. A lack of awareness of the need to see a rheumatologist from the patient and the primary care physician may therefore limit early diagnosis of RA. This was also the case in the United Arab of Emirates (Zafar et al., 2012), this could be overcome by increasing patients’ awareness and by anticipation of awareness programs and public campaigns.

Only 9.4% of our patients were smokers which were lower than that reported in the COMORA study (13.2%) (Dougados et al., 2014); this can be explained by the community traditions in revulsion of cigarette smoking among females who represented the vast majority of our patients. 24.9% of patients with subcutaneous nodules were smokers while only 16.4% were nonsmokers (P = 0.001), this is in agreement with a study on USA RA patients where Saag KG et al (Saag et al., 1997) reported that Pack cigarette smoking was associated with subcutaneous nodules (P = 0.051), also this was in line with Nyhäll-Wåhlin et al (Nyhäll-Wåhlin et al., 2006) who stated that in Sweden RA patients smoking was associated with rheumatoid nodules (P < 0.001), moreover 34.5% of patients
having hand erosions at diagnosis were smokers vs 30.5% nonsmokers (P = 0.225), this is in line with Yin et al (Yin et al., 2017) who stated that there was no association between smoking status with the presence of radiographic erosions (P = 0.66).

Regarding comorbidities, 8.2% of patients were diabetics and 2.8% had hypertension which appear to be lower than frequencies observed in the general Egyptian population (15.5% for diabetes, 26.3% for hypertension) (Ashour et al., 1995; Hegazi et al., 2015), also this is lower than frequencies reported by Alian et al, 2017 (Alian et al., 2017) where 32.2% of the Egyptian RA patients recruited in that study were hypertensive and 20.1% were diabetic, again our frequency was lower than that reported by Al-Bishri et al, 2013 (Al-Bishri et al., 2013) in a study conducted on 340 RA patients where 31% of patients were diabetic and 36% had hypertension, this may be explained by the high percentage of corticosteroids intake among the patients of the latter 2 studies (87.1% and 80.8%, respectively), while it was only 45% in our patients, we could not discuss these comorbidities in relation to cardiovascular complications of RA despite its importance in Egyptian RA patients (Elshereef et al., 2015) due to shortage of data in the registry files regarding this point which is one of the limitations we faced. In addition, the association between RA and periodontitis could not be assessed due to lack of documented data regarding this aspect in the registry files.

The main reported extra-articular manifestations in our RA patients were SNs (14.2%) and 2ry SS (10.5%), which is lower than other populations, e.g., in the Brazilian population (SNs (19.4%) and 2ry SS (46.9%)) (Almeida Mdo et al., 2014), in Turkish patients (18.1% for SNs) (Calguneri et al., 2006), in the United Arab of Emirates (2ry SS 28%) (Badsha et al., 2008) and in Omani patients (2ry SS 24.4%). ILD was reported in 0.8% of our RA patients, which was lower than that reported in Saudi Arabian RA patients (2.7%) (Al-Bishri et al., 2013) and Omani RA patients (3%) (Al-Temimi, 2010); this may be attributed to our previous relying on the less accurate conventional radiography for diagnosis of ILD due to high expenses of high resolution CT chest.

Compared to other countries, Egyptian patients seem to have less erosive disease (20.6%) at disease diagnosis vs. 68.1% in Algeria (Slimani et al., 2014), 62.2% in Brazil (Almeida Mdo et al., 2014), 55.2% in the United Arab Emirates (Badsha et al., 2008), and 42% in Kuwaiti patients (Al-Salem and Al-Awadhi, 2004) denoting earlier diagnosis and the effect of anticipation of support groups, awareness programs, and public campaigns similar to efforts anticipated in the United Arab of Emirates (Zafar et al., 2012).

Around 52% of patients were positive for RF which was close to the Brazilian population (49.2%) (Almeida Mdo et al., 2014; Da Mota et al, 2010), while it was less than Kuwaiti, Omani, Saudi Arabian, and Sweden patients, where it was 60%, 76%, and 73%, respectively (Al-Bishri et al., 2013; Al-Salem and Al-Awadhi, 2004; Al-Temimi, 2010; Hallert et al., 2014).

Methotrexate was the most commonly used DMARD; where it was received by 82.8% RA patients while it was in the Saudi Arabian (74.4%) (Al-Bishri et al., 2013), Algerian patients (72.2%) (Slimani et al., 2014), and in the COMORA study (88.6%) (Dougados et al., 2014). None of our patients were on biologic therapy that could be attributed to the financial problems in our country; making treatment with conventional DMARDs compulsory although the rate of biologic use in clinical practice is rising to treat moderate to severe RA that has not responded to conventional DMARDs.
In the present study, time trend analysis revealed a significant annual increase by 0.13% in the newly diagnosed RA cases (P = 0.017) which may reflect increase in patients’ medical awareness and improvement of medical service in our country during the last 20 years.

We detected a significant annual decrement by 0.4% in female RA patients (P = 0.02) which was less than that recorded in a study done on 446 RA patients from Olmsted County, Minnesota where there was a modest increase in women from 1995 to 2007 by 2.5% (P = 0.02) (Myasoedova et al., 2010).

Our study revealed a significant annual increase in the mean age of disease onset by 0.2 year (P < 0.001). Concordantly, in a study conducted on 566 Japanese patients from 1960 to 1990; the age of onset increased significantly from 37.5 to 46.9 years. This increase may reflect changes in health measures (e.g., increase in life span and change in socio-economic status) (Imanaka et al., 1997).

Polyarticular pattern of joint affection at disease onset was the most commonly detected (80.3%) among our RA patients who were in concordance with that reported in literature (Hecht et al., 2015), but it showed significant decline annually. While there was a statistically significant annual increase in both monoarticular and oligoarticular presentations which may be explained by the earlier diagnosis of arthritis patients in the last decade.

An interesting finding in our data was the steady annual decline in number of cases with bony hand erosions at diagnosis by 0.5% (P = 0.01) denoting earlier diagnosis and more tight disease control and anticipation of support groups, awareness programs, and public campaigns similar to efforts anticipated in the United Arab of Emirates (Zafar et al., 2012).

In our study, there was no statistical difference between males and females regarding the presence of hand erosions [33% of the studied RA females (n = 2774) had erosions, while 29% of males had erosions (P = 0.39)], which was statistically comparable with results of the quantitative standard monitoring of patients with RA (QUEST-RA) program which was established to include 6004 RA patients from 70 sites in 25 countries where women had erosions more often than men (P = 0.36) (Sokka et al., 2009). Also, number of RF positive cases was significantly higher in the erosive group which was in agreement with previous studies (Hecht et al., 2015; Van Steenbergen et al., 2014).

Our study has several limitations: first, this is a retrospective study where shortage of some important data documented in the registry files was a major obstacle in our research, second; patients were included using the 1987 ACR criteria for RA diagnosis instead of the new 2010 ACR/EULAR criteria, this is because we studied patients diagnosed from 1995 and we wanted to compare RA Egyptian patients with RA cases from previous studies which also relied on the older criteria. The third limitation was that ACPA test was done for only 269 (8.3%) patients due to financial causes. Also although cardiovascular disease is an important comorbidity (Elshereef et al., 2015) we could not document its percentage or correlate it with other comorbidities as DM, hypertension due to lack of data in the registry files regarding this point. Furthermore, the association between RA and periodontitis could not be assessed due to lack of documented data regarding this aspect in the registry files.

The changing referral patterns and change in awareness of the public and primary care physicians/providers about RA (Zafar et al., 2012) is one of the most important factors that influenced our research.
**Conclusion**

The present study describes RA characteristics in a tertiary referral hospital, carried on a large cohort of Egyptian patients over a long period of time (2 decades). We found a female predominance, younger age at disease onset, lower frequency of extra-articular manifestations, more frequent polyarticular pattern at disease onset and less erosive disease.

This 20 year follow-up cohort has demonstrated that during a period of changing referral patterns and earlier disease recognition, earlier diagnosis, improved disease control, and fewer signs of disease progression (i.e., erosions) are found in Egyptian RA patients. Some conclusions about the cultural and ethnic comparisons would be important as well.

**Ethical approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

**References**


