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From Symptoms to Diagnosis: An Observational Study of the Journey of Rheumatoid Arthritis Patients in Saudi Arabia

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ABSTRACT

Objectives: Rheumatoid arthritis (RA) is often not diagnosed or treated quickly enough to alter outcomes. We aimed to evaluate the lag times from disease onset to first clinical consultation and diagnosis and to identify factors contributing to delayed diagnosis in Saudi Arabia. ***Methods***: This retrospective, multicenter study collected data on 250 patients, from six hospitals in Saudi Arabia, who met the 2010 American College of Rheumatology criteria for RA. ***Results:*** The patients mean age was 43.3±12.0 years (mean disease duration: 6.6±5.8 years). The majority were female (84.8%) and presented with joint pain during RA onset (83.6%). On average, they consulted 4.3±2.5 physicians from the first symptoms to the final diagnosis. The mean time from onset to first physician visit (lag 1) was 6.2±5.5 months, whereas the mean time was 30.2±16.0 months between the initial visit and final RA diagnosis (lag 2). Only 3.2% of patients initially sought consultation from a rheumatologist, while 67.2%, 23.6%, and 6.0% first met with orthopedic surgeons, general practitioners, and non-rheumatologists, respectively. Non-rheumatologists offered diagnoses in 24.4% of cases while rheumatologists diagnosed 75.6%. The absence of early hand/wrist involvement and fatigue were associated with delayed RA diagnosis (long lag 2; $p<0.010$). Moreover, geographic distribution influenced RA diagnosis, with rural patients experiencing a greater delay than urban patients ($p<0.0001$). ***Conclusions:*** Failure of patients to be seen by rheumatologists at RA onset delayed diagnosis and treatment. Thus, RA diagnosis can be accelerated by encouraging early referral to rheumatologists.

Early diagnosis and treatment have become primary objectives for rheumatologists and clinicians who manage patients with rheumatoid arthritis (RA). Rheumatoid inflammation begins early and is progressive in nature,[1] ultimately resulting in substantial risk of progressive joint damage, disability, and an increased morbidity rate. In fact, 70% of patients develop erosion after three years,[2] which suggests that there exists a "window of opportunity" during which appropriate therapies could be delivered to substantially alter patients' outcomes. Numerous studies have indicated that as little as a 12-week delay in therapy initiation can adversely affect disease activity, remission, functional capacity, and radiographic progression.[3–11] There has been a shift in the therapeutic paradigm of RA; it is now generally thought that disease-modifying antirheumatic drug (DMARD) therapy should be started as early as possible, preferably within three months of RA onset.[3–11] Nevertheless, early treatment is unrealistic for most RA patients in the absence of adequate educational, triaging, and referral systems as studies analyzing the time from symptom onset to delivery of DMARDs have reported significant delays.[12–21]

Furthermore, several studies from around the world have started to investigate the reasons for delayed diagnosis in RA patients.[12,13] In Saudi Arabia's

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case, the exact reasons leading to late diagnosis of patients with RA remains unknown.[14] It is possible this results from postponed consultations with specialists due to the insidious nature of RA which means that non-rheumatologists routinely perform RA patient consultations.

Determining the factors that might lead to late diagnosis and treatment of Saudi Arabian RA patients could ultimately contribute to improved outcomes nationally and internationally. Therefore, it is critical that we gain a detailed understanding of the RA patient's journey. This can be divided into three main stages: onset of symptoms to consultation, consultation to diagnosis, and diagnosis to proper RA treatment.

In our study, we analyzed the distinct stages of the RA patient journey to assess the lag time from disease onset to first clinical consultation and diagnosis and worked on identifying factors that contribute to delayed RA diagnosis.

METHODS

Our retrospective, cross-sectional, multicenter, hospital-based study was conducted between June 2012 and April 2013. A total of 250 consecutive patients who attended the outpatient clinic at six hospitals in Saudi Arabia were included in the study. Patients had to meet 2010 American College of Rheumatology criteria for RA and be aged 18 years old or more and demonstrate a willingness to participate in the study to be included. Patients who refused to participate, had incomplete data in their charts, and/or were aged under 18 were excluded. A total of four cases were excluded due to incomplete clinical data in medical records.

Our investigation followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was conducted in accordance with the Declaration of Helsinki. The local ethics committee approved the study.

The patients' records were reviewed, and interviews were conducted by research nurses and a trained patient support team with a medical background (either physicians or pharmacists). To eliminate interviewer bias and ensure consistency, interviewers received standardized training for the interview questions. The following patient attributes were assessed through medical records and patient interviews: patients demographics including age, gender, marital status and education was recorded. Other relevant clinical data (including disease duration), the time between first symptom and first medical encounter (lag 1), the nature of first symptoms (joint pain, stiffness, body ache, fatigue, fever, other symptoms), and the part of the body first affected by initial symptoms (hand, wrist, foot, knee, shoulders, others) was also recorded. Additionally a record of the patient's first visit to a specialty doctor, the specialty of the doctor who made the definite diagnosis of RA, lag time between first medical encounter until definite diagnosis (lag 2), and the number of doctors visited between the first medical encounter until the final diagnosis was made.

The first medical encounter for RA-related symptoms was determined from the patient and medication history present in the medical charts, and the first diagnosis of RA was defined as the first time the caring physician recorded in the chart that the patient had RA. The recorded date of diagnosis was compared to the dates mentioned by patients during interviews to confirm the date of reaching a clear diagnosis. If the exact date of symptom onset or first medical encounter could not be determined, the corresponding intervals were treated as censored data. Any clinical features not mentioned in the written records were treated as unavailable.

The descriptive statistics collected included mean, range, standard deviation (SD), and percent distribution of variables.

Based on previous data published by Gray and Nuki,[15] we expected that less than 20% of our patients would be treated within three months of symptom onset. Therefore, we determined that a sample size of 246 patients was required (95% confidence interval [CI] of 0.100).

Two-tailed analysis was used, and statistical significance was assigned when type-I error probability was ≤ 5% ($p<0.050$). The correlation between lag 2 and the binary variables (e.g., gender, presence of fatigue) was calculated using point-biserial correlation. The correlation between continuous variables was assessed using Spearman's correlation.

The following variables were included in the analysis: age, gender, specialty of first consultation (rheumatologist or non-rheumatologist), number of doctors visited before diagnosis, geographic area (urban, rural), nature of the first symptom, hand and wrist involvement, and the presence of fatigue. SPSS

Statistics (SPSS Inc., Chicago, US) version 18 was used for all statistical analysis.

A systematic review of the literature revealed a total of 22 studies published between 1994 and 2012 that analyzed times between RA symptoms' onset and first visit to a physician and/or onset of symptoms of RA and initiation of DMARDS.

RESULTS

Patients had a mean age of 43.3±12.0 years and an average disease duration of 6.6±5.8 years. Notably, the majority of these patients were female (84.8%). Most patients (83.6%) presented with joint pain during RA onset, and almost half (49.2%) showed symptoms of fatigue. Fewer patients presented with foot/knee arthritis, isolated foot monoarthritis, or knee monoarthritis as the first symptom. Moreover, analysis revealed that these patients consulted an average of 4.3±2.5 physicians between their first RA symptom and final diagnosis with a range of 1–15 doctors [Table 1].

The first physicians visit occurred approximately 6.2 months after RA onset (lag 1), whereas the mean duration of initial physician visit and final RA diagnosis (lag 2) was around 30 months [Table 2]. Only 3.2% of patients initially sought consultation by rheumatologists, while 67.2%, 23.6%, and 6% sought the opinion of orthopedic surgeons, general practitioners (GPs), and other non-rheumatology specialties, respectively. However, these non-rheumatologists were only able to provide positive RA diagnoses in approximately one-fourth of cases. Rheumatologists gave the final RA diagnoses for the majority of patients (75.6%).

We also sought to determine which patient characteristics might be related to an increased delay in the time from onset to RA diagnosis (lag 2). Patients with early involvement of the hand/wrist showed less delay in diagnosis compared to patients with non-classical initial RA symptoms (28.8±14.7 months vs. 35.7±19.6 months, $p = 0.007$). Additionally, the presence of fatigue as an initial symptom was significantly associated with earlier diagnosis ($p = 0.012$). Patients living in urban regions were diagnosed earlier than those in rural areas ($p<0.0001$). Delay in seeking medical advice (lag 1) was another factor associated with a delay in diagnosis ($p = 0.013$). However, there was no significant association with gender and age [Table 3].

Table 1: Demographic data of the patients included in the study.

Patient characteristics	All patients (n = 250)
Age (years)*	43.3±12.0
Gender (% female)	84.8
Disease duration (years)*	6.6±5.8
Joint pain at first onset (%)	83.6
Fatigue and generalized body ache at first onset (%)	49.2
Foot or knee arthritis at first onset (%)	40.5
Isolated foot monoarthritis at first onset (%)	9.8
Knee monoarthritis (%)	3.3
Average number of doctors visited*	4.3±2.5

**Data presented as mean±SD.*

Table 2: Analysis of initial clinical consultation, diagnosis, and treatment of patients with RA.

Patient characteristic	Patients (%)
Initial consultation	
Orthopedic surgeons	67.2
General practitioners	23.6
Non-rheumatologists	6.0
Rheumatologists	3.2
RA diagnosis	
Non-rheumatologists	24.4
Rheumatologists	75.6
Lag periods*	
Lag 1 (months)	6.22±5.53
Lag 2 (months)	30.2±16.0

*RA: rheumatoid arthritis; lag 1: time from the first symptom to physician consultation; lag 2: time from onset to RA diagnosis. *Data presented as mean±SD.*

Table 3: Factors affecting delayed RA diagnosis.

Variables	Months (mean±SD)	r	*p*-value
H/W involvement*			
Yes	28.8±14.7	0.171	0.007
No	35.7±19.6		
Gender*			
Male	28.1±15.8	0.055	0.390
Female	30.6±16.0		
Fatigue*			
Yes	27.6±14.7	0.159	0.012
No	32.7±16.9		
Region*			
Urban	27.8±14.9	0.252	<0.0001
Rural	37.0±17.1		
Lag 1**	6.22±5.53	0.173	0.013
Numbers of doctors visited**	4.3±2.5	0.547	<0.0001
Age**	43.3±12.0	0.105	0.134

RA: rheumatoid arthritis; r: correlation coefficient; H/W: hand and wrist; lag 1: time from the first symptom to physician consultation.
**point-biserial correlation test; **Spearman correlation test.*

DISCUSSION

We found that patients consulted an average of four physicians between their first RA symptom and final diagnosis, with a mean time from first physician visit to final RA diagnosis of approximately 30 months. Although patients consulted with physicians at around seven months after the onset of RA symptoms, very few subjects initially sought a consultation with rheumatologists, who were ultimately responsible for diagnosing most patients with RA. Correlation analysis revealed that the absence of initial symptoms (i.e., fatigue, hand/wrist involvement) and geographic region (rural vs. urban areas) were associated with delayed diagnosis.

In recent years, a transformation in the therapeutic approach of RA has occurred, and it is now generally accepted that DMARD therapy should start as early as possible.[3–11] Nevertheless, there is little known about when treatments are initiated in routine clinical practice. Studies analyzing the time from symptom onset to delivery of DMARD therapy have reported significant delays, which range from six to 57 months, depending on the geographical region.[12,13,15–21] Notably, deferred treatment could be attributed to the patients (by delaying presenting to a family physician),[22] primary care,[15,16,21,23] physicians (lack of experience in recognizing inflammatory arthritis and delay in referral to specialists),[15,16,21,23] or specialists (long waiting list and delay in initiating therapy). Alternatively, these delays can result from the fact that identification and diagnosis of RA is difficult due to the insidious nature of the disease and the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), which have the potential to mask RA symptoms.[24] Also, the absence of early pathognomonic features could represent a contributing factor,[16,24] which is supported by our findings. Similar to previous studies,[15,16,21] our findings suggest that delayed specialist referrals constitute a principal reason for late diagnosis and subsequent treatment in Saudi Arabia. Nevertheless, the cause for postponed treatment in RA patients is likely to be multifactorial. Therefore, further investigation of how unique factors can lead to increased lag times is warranted in Saudi Arabia and other countries.

Several studies from around the world have analyzed the distinct lag times between disease onset and first clinical consultation or diagnosis for RA patients. In fact, Stack et al,[25] performed a systemic review of the literature and found that in some countries (e.g., the UK) only half of the patients with RA consulted with healthcare professionals within 12 weeks of symptom onset. However, in other countries (e.g., Austria, Germany, and The Netherlands) shorter delays in physician consultation were reported. In Saudi Arabia, we found that the postponement of care was much longer compared to other regions (6.2 months). Interestingly, the time required to consult with any physician in Saudi Arabia was similar to the time from symptom onset to the first visit to a specialist (i.e., rheumatologists) in Spain (6.3±11.3 months)[26] and the USA (5.5–8.4 months).[16,27,28] Interestingly, in Spain, the faster consultation with specialists led to a mean treatment initiation time of 4±13.5 months from the first visit,[26] whereas it took approximately 30 months to receive a diagnosis in Saudi Arabia (lag 2). Although measures are required for improving lag 2 in Saudi Arabia, it must be noted that some countries display even longer lag 2 times. For example, Rodríguez-Polanco et al,[13] reported a 40.5-month delay between symptoms' onset and diagnosis in a retrospective study conducted in Venezuela. Their study reported lag times of 16.3 and 23.9 months between symptoms' onset and first consultation with a physician or first consultation and diagnosis, respectively. Like our study, a definitive diagnosis of RA was made by rheumatologists for the majority of patients (92.3%). Cho et al,[29] described a 42-month lag 2 period in Korea, which was interesting considering that the time from symptom onset to rheumatology referral was only about six months. This study suggested that a reduction in the use of unconventional health care (i.e., private sector and non-regular referrals) could improve RA management in Korea. In sharp contrast to these reports, investigations conducted in Europe, the United Arab Emirates (UAE), and Malaysia found lag 2 times of 6, 7.8, and up to 12 months, respectively.[20,30] Our study represents an important step towards understanding the patterns of RA diagnosis in Saudi Arabia, and how they fit into the current international landscape of RA management. Thus, this analysis can contribute to shortening the relatively large delays in RA diagnosis observed in Saudi Arabia.

In our study, the absence of initial symptoms (fatigue and hand/wrist involvement) and geographic region (rural vs. urban areas) were associated with the delay in RA diagnosis, whereas gender and age

were not. Recent literature supports that not only the lag times but also the factors that contribute to enhanced treatment vary widely by country or region. For this reason, future studies must examine a broad range of factors to identify the differential variables that might contribute to improving RA management within diverse regions or populations.

Interestingly, as mentioned above, recent progress seems to have been made to decrease the lag times experienced by RA patients. In fact, Irvine et al,[31] reported a progressive drop in the delay between symptoms' onset and GP referral in the UK (before 1986, 21 months; 1987–1989, 23 months; 1990–1993, seven months; 1994–1997, four months; $p<0.030$), as well as in the delay from first rheumatology visit to the start of DMARD therapy (before 1986, 32 months; 1987–1989, 21 months; 1990–1993, eight months; 1994–1997, one month; $p<0.001$). Moreover, the number of patients given DMARD treatment within six months of symptom onset increased from 5% (before 1994) to 44% (1994–1997). Therefore, it appears that patients are being referred earlier in their disease course, and DMARDs are prescribed sooner. A similar trend was observed in Spain measured over two decades (−4.59±0.2 months by year; $p<0.001$).[32] This improvement was reported to stem from a reduction in the time to first specialist visit after onset.[32] Additionally, Zafar et al,[20] detected a mean reduction of 45.8% in the lag time from symptom onset to diagnosis (14.4±15.6 to 7.8±12.1 months; $p = 0.001$) in the UAE between 2006 and 2010. They suggested that this decrease in lag time might be due to the inception of patient support groups and enhanced public RA awareness. In New Zealand, the median time from symptom onset to therapy was 6.1 months, but alterations in triage allocation to consider RA cases as urgent led to earlier patient treatment (a difference of 97 days, $p = 0.003$).[19]

Our observational study has some limitations: primarily, the possibility that patients may have inaccurately recalled the exact date of symptoms' onset, which could have influenced our study outcomes. However, measures were taken to minimize this potential problem. First, they used experienced patient support specialists to interview the patients and identify accurate dates regarding RA symptom onset. Second, interviewers used major national and local events to define the patients' perceived date of disease onset to minimize variations in estimating patient delay. It is also possible that not all factors influencing the delay in RA diagnosis were included in this analysis. The conclusions of this investigation are consistent with recent reports of similar journeys in many other countries.

CONCLUSION

Our findings, along with others from various regions around the world, collectively indicate that delay in RA diagnosis and management may stem from slow diagnosis by physicians rather than postponed medical consultation by patients. This may be because patients with RA often do not seek the advice of rheumatologists at the onset of their symptoms and non-rheumatologists fail to refer RA patients to rheumatologists soon enough. Thus, further studies are warranted to determine if the failure to seek the advice of rheumatologists is driven by lack of patient understanding regarding the role of specialists in their care, poor referral efforts by the non-rheumatologists, or difficult access to rheumatologists in Saudi Arabia. Nevertheless, it appears that establishing a system of early referral to specialists by non-rheumatologists could accelerate RA diagnoses.

Disclosure

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