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The Time Lag Between the Onset of Symptoms and Diagnosis of Ankylosing Spondylitis in Sulaymaniyah Province, Iraq

Raouf Rahim Merza[1], **Lawen Jamal Mustafa**[2*]

[1]Sulaimani Medical School, University of Sulaimani, Kurdistan Region, Iraq
[2]Ministry of Health, Sulaimani, Kurdistan Region, Iraq

***Corresponding Author:** Lawen Jamal Mustafa, Ph.D., Rheumatologist, Ministry of Health, Sulaimani, Kurdistan Region, Iraq. Tel: +964-7718339337, Email: jamallawen4@gmail.com

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic, progressive, and disabling disease among rheumatological diseases.

Objectives: Current study aimed to investigate the Time lag between the onset of symptoms and final diagnosis of AS, and also identify the factors that contribute to that delay in Sulaymaniyah province.

Methods: In this cross-sectional study, 104 (AS) patients who satisfied the modified New York 1984 criteria were enlisted. The time lag was defined as the diagnosis delay (DD) between the appearance of the first symptoms and the correct diagnosis of AS. Spearman correlation analysis was used to detect correlations between variables.

Results: The higher percentage of variables with DD ≥ 6 years were urban 32 (74.4%), housewife 15(34.9%), had no family history 42 (97.7%), with high diploma 33 (76.7%), and positive HLAB27 31 (72.1%), the first specialist consulted orthopedics 21(48.8%) then GP 6 (14.9). Moreover, the higher percentage of variables with DD < 6 years were diagnosis years between 2000 to 2020, rural 55 (90.2), 39 (63.9%) respectively, higher education 47 (77%), employee and worker 22 (36.1%), positive family history 44 (72.1%), positive human leukocyte antigen (HLAB27-61) (100%), inflammatory back pain 47 (77%), rheumatologist 29 (47.5%). The average year's DD is 6.48. A statistically significant positive correlation was detected between the DD and age, age at diagnosis but, a negative correlation was found between the DD time and, age at symptom onset.

Conclusion: The Time lag between the onset of symptoms of AS and the final diagnosis in Sulaymaniyah was 6.48 years. (HLA-B27), age, age at diagnosis, education level, occupation, 1st specialist, 1st symptom at onset of disease and family history are the factors that affect delayed diagnosis in Sulaymaniyah patients with AS.

Keywords: Ankylosing Spondylitis, Delay Diagnosis, Rheumatology, Spondyloarthritis

1. Background

Ankylosing spondylitis (AS) is a member of the spondyloarthritis (SpA) group of disorders.[2] Among the illnesses connected to spondyloarthropathy include reactive arthritis, psoriatic spondyloarthritis (PsA), inflammatory bowel disease spondyloarthritis, and undifferentiated spondyloarthritis.[2]

Even though AS patients should receive early diagnosis and treatment than can prevent its harmful consequences, it is not possible to estimate early and timely diagnosis of the disease by patients. Considering the recent advances in the treatment of this disease. A disease's early diagnosis is crucial. Because the delay in allocation can lead to irreparable structural damage to the spine.[3] About 0.2-1.2% of people are estimated to have AS. Infancy is when this illness first manifests itself. and has a great financial burden on society.[4-7] Also, patients' quality of life may decline as a result of the delayed diagnosis. and the workforce may be lost. Moreover, due to this circumstance, health service resources are being used ineffectively and the diagnostic process is taking too long.[4,5]

Determining the elements involved in the delayed diagnosis of AS can help to develop accurate clinical guidelines. Various factors such as female gender, younger age at the onset of symptoms, HLA-B27 negativity, the presence of enthesitis or enthesitis pain, no family history of SpA, older age at diagnosis, the absence of peripheral arthritis or dactylitis, and the presence of psoriasis have been introduced as reasons for diagnostic delay in previous studies.[6]

2. Objectives

This study was conducted with the objective to find out the first symptoms of patient such as (Inflammatory back pain, Enthesitis, Knee pain, Peripheral joint involvement, Uveitis), and after how long they have been diagnosed as Ankylosing spondylitis. Also find out the number of factors related to the diagnosis delay of ankylosing spondylitis.

3. Methods

In this cross-sectional study, 104 patients (female, male), with a diagnosis of AS according to Modified New York criteria[7] were recruited. The study used information gathered from the rheumatology department at Shahid Hemn Teaching Hospital in Sulaimani, Kurdistan/Iraq, between September 2021 and April 2022 from patients who can provide informed consent and who are between the ages of 18 and 65. Patients older than 65 or younger than 18 who refused to provide informed consent were also excluded from the study. This work has been done in line with the STROCSS criteria.[8]

3.1. Diagnosis of Ankylosing Spondylitis

The rheumatologist, internal medicine, orthopedics, and other specialists have diagnosed the patients. All patients were diagnosed previously and had been reviewed and the diagnosis was confirmed with modified New York criteria.[7]

3.2. Sample Size Calculation

Since the design of the study is cross sectional study and one group. The below equation was used;

$n = (Z\alpha)2 * P (1 - P)/ d2$.The total sample size was = 104 cases. n = the sample size, P = prevalence of the variable under the study, d = the difference the investigator wishes to detect, $Z\alpha = 1.96$

3.3. Data Collection

Convenient sampling was used to collect the enrolled data. We used a questionnaire to take medical history face to face. It contained questions about age at onset of AS symptoms, gender, disease duration, education level, various aspects of the disease like morning stiffness duration, alternating buttock pain, inflammatory back pain, and the specialist that first consulted. The time lag is defined as the diagnosis delay (DD) between the onset symptom of AS and the final diagnosis. HLA-B27 was obtained from the patient medical record. A radiology expert examined every patient's sacroiliac joint MRI.

3.4. Statistical Analysis

Statistical analyses were conducted using the software Statistical Package for the Social Sciences (SPSS for Windows, version 22.0, SPSS Inc., Chicago, IL, USA) program. The mean and standard deviation of variables was used for determining continuous variables. percentage and numbers were used for determining discrete variables. Normality distribution was analyzed by the Kolmogorov-Smirnov test. We used the median of diagnosis delayed to compare the patient's characteristics (median = six years). An Independent student *t* test was implemented to compare means between two groups. Differences with $P < 0.05$ were considered statistically significant. Spearman correlation analysis was used to detect correlations between DD variable with other variables such as age, Age at diagnosis, Age at symptom onset, HLA B27 and diagnosis decade.

4. Results

The study consisted of 104 patients (72 males and 32 females). The average ages were 37.72 (range 21–59). All patients who met the modified New York criteria were made aware of the study's aim and purpose.

The average age of patients at symptom onset was 23.13 (range 10–42) with an average year's DD is 6.48. The average age at diagnosis was 29.60 (range 16–52), The delayed diagnosis was 6.18 and 7.29 in men and women, respectively.

Some demographic data of patients are shown in Table 1. There were no significant differences in the distribution of gender, diagnostic decade, age at symptom onset, 1st symptom at onset of disease, specialist give final diagnosis, and residency. specialist giving a final diagnosis, and residency. The higher percentage of variables with delayed diagnosis ≥ 6 years were urban 32 (74.4%), housewife 15 (34.9%), had no family history 42 (97.7%), with high diploma 33 (76.7%), and positive HLAB27 31 (72.1%), the first specialist consulted orthopedics 21(48.8%) then GP 6(14.9).

Moreover, the higher percentage of variables with delay diagnosis < 6 years were diagnosis years between 2000 to 2020, rural 55 (90.2), 39 (63.9%) respectively, higher education 47 (77%), employee and worker 22 (36.1%), positive family history 44 (72.1%), positive HLAB27- 61 (100%), inflammatory back pain 47(77%), rheumatologist 29 (47.5%). The average time between the onset of the first symptoms at the onset of the disease and the final diagnosis was 6.48 years. A statistically significant positive correlation was detected between the DD and age ($r = 0.581$, $P < 0.001$), age at diagnosis ($r = 0.567$, $P < 0.001$), a significant negative correlation was found out between the DD time and, age at symptom onset ($r = 0.017$, $P = 0.433$) (Table 2).

5. Discussion

In this study, we identified the average DD of 6.48 years among AS patients in a Sulaymaniyah population. However, the diagnostic delay was shorter in the male patients with more education, last ten years 2000-2020, and inflammatory back pain. Higher age at diagnosis significantly prolonged the time it took to diagnose AS.

Accumulating evidence showed that the delayed diagnosis of AS ranges from six to 10 years. Our findings of diagnostic delay of six years in the Sulaymaniyah population are from previous studies conducted in Iran,[9] the UK,[10] Germany,[11] sought Korea,[12] and Japan.[13] However, in one study conducted in Turkey the mean delay time in diagnosis was 3.28 ± 3.32 years.[14] The average delay time of diagnosis in the Turkey, population may be related to the type of population and the center for recruiting patients. In that study, patients were recruited in a hospital that provides health services mainly to military personnel regularly their health status is examined. Early diagnosis and cessation of the pathological progression of AS, as an insidious disease is very important for slowing down disease progression because it can impair the quality

Table 1. Characteristics of Patients With Axial Spondyloarthritis Stratified by the Delay in Diagnosis

Variables		Delay to diagnosis < 6 years No. (%)	Delay to diagnosis ≥ 6 years No. (%)	Total N0. (%)	*P* Value*
Sex	Female	16 (26.2)	16 (37.2)	32 (30.8)	0.53
	Male	45 (73.8)	27 (62.8)	72 (69.2)	
Age	Age, years	61 (Mean = 33.43)	43 (Mean = 43.81)	104 (Mean 37.72)	0.0001
	Age at symptom onset, years	61 (Mean = 22.61)	43 (Mean = 23.51)	104 (Mean = 23.13)	048
	Age at diagnosis, years	61 (Mean = 26.59)	43 (Mean = 33.86)	104 (Mean = 29.60)	0.0001
Diagnosis decade, years	Before 2000	1 (1.3)	3 (7.0)	4 (3.8)	0.132
	Between 2000-2010	5 (8.2)	11 (25.6)	16 (15.4)	
	Between 2010-2020	55 (90.2)	29 (67.4)	84 (80.8)	
Residency	Rural	39 (63.9)	11 (25.6)	50 (38.7)	0.084
	Urban	22 (36.1)	32 (74.4)	54 (68.3)	
Education level	Illiterate	1 (1.6)	4 (9.3)	5 (4.8)	0.031
	≤ Diploma	13 (21.3)	6 (14)	19 (18.3)	
	> Diploma	47 (77)	33 (76.7)	80 (76.9)	
Occupation	Housewife	9 (14.8	16 (34.9)	25 (23.1)	0.024
	Employee	22 (36.1)	12 (27.9)	34 (32.7)	
	Student	8 (13.1)	1 (2.3)	9 (8.7)	
	Worker	22 (36.1)	14 (31.9)	36 (35.6)	
Family history	Yes	44 (72.1)	1 (2.3)	45 (17.3)	0.001
	No	17 (27.9)	42 (97.7)	59 (82.7)	
HLAB27	Yes	61 (100)	31 (72.1)	92 (88.5)	0.001
	No	0 (0.0)	12 (27.9)	12 (11.5)	
1st symptom at onset of disease	Inflammatory back pain	47 (77.0)	23 (53.5)	70 (67.3)	0.023
	Enthesitis	2 (3.3)	1 (2.3)	3 (2.9)	
	Peripheral arthritis	12 (19.7)	14 (32.6)	26 (25.0)	
	Uveitis	0 (0.0)	3 (7.0)	3 (2.9)	
	Cervical pain	0 (0.0)	2 (4.7)	2 (1.9)	
1st Specialist consulted	Internist	8 (13.1)	3 (7.0)	11 (10.6)	0.034
	Orthopedics	14 (23.0)	21 (48.8)	45 (48.1)	
	GP	1 (1.6)	6 (14.0)	7 (6.7)	
	Rheumatologist	29 (47.5)	2 (4.7)	31 (21.4)	
	Ophthalmologist	0 (0.0)	3 (7.0)	3 (2.9)	
	Gastroenterologist	1 (1.6)	0 (0.0)	1 (1.0)	
	Nephrologist	3 (4.9)	2 (4.7)	5 (4.8)	
	Neurologist	2 (3.3)	2 (4.7)	4 (3.8)	
	Neurosurgeon	3 (4.9)	4 (9.3)	7 (6.7)	
Specialists give a final diagnosis	Internist	1 (1.6)	0 (0.0)	1 (1.0)	0.514
	Orthopedics	1 (1.6)	1 (2.3)	2 (1.9)	
	Rheumatologist	58 (95.1)	41 (95.3)	99 (95.2)	
	Ophthalmologist	0 (0.0)	1 (2.3)	1 (1.0)	
	Neurologist	1 (1.6)	0 (0.0)	1 (1.0)	

Abbreviations: HLA, Human leukocyte antigen; GP, general practitioner.
* Chi-square test and independent sample *t* test were used.

of life (QoL) with functional and structural limitations.[15] Several highly efficacious therapies have become available in recent years. One of the main factors for the delay in diagnosis is that in many patients with AS, the radiographic results are normal even after several years after the onset of inflammatory back pain.[16] Due to the less sensitivity and specificity of radiographic sacroiliitis,[17,18] According to new classification criteria by the Assessment of Psoriatic Arthritis International Society (ASAS), MRI has been used for early diagnosis of SpA, including AS. MRI has been suggested as the most sensitive method for detecting sacroiliitis.[19] Therefore, in our study high number of

Table 2. The Relationship Between Factors Related to the Diagnostic Delay Time

Factors	r	*P* value
Age	0.581	<0.001*
Age at diagnosis	0.567	<0.001*
Age at symptom onset	0.017	0.433**
Diagnosis decade	-0.182	0.065**

*Correlation is the significant at the 0.01 level.
** Correlation is the significant at the 0.05 level.

patients with 55 (90.2), DD was less than 6 years.

We found that patients with delayed diagnoses of less than six years were more educated. In a study by Song et al, health-related (QoL) and its predictors in patients with AS in Southwest China were investigated.[20] They found that AS patients with higher educational levels showed higher physical component summary scores of Short Form (SF-36), In another study, According to reports, those with chronic illnesses and low educational levels experienced more issues than those with high levels of education.[21] In a cross-sectional study, it was suggested that AS patients with a lower educational level had poor physical function QoL.[22] Previous studies suggest that a higher educational level positively affects QoL. Higher education results in better income, career choice, and disease management, which improves health-related (QoL).[23] Similar to our findings. Dincer et al[24] and Gerdan et al[25] reported a higher mean of DD in patients with low educational levels compared to high educational level patients. In contrast, in another study by Ibn Yacoub et al, the educational level did not affect DD.[26]

Another factor related to AS in our study was the age of the participants. The mean age of patients with AS was 37.72. According to the literature, the condition primarily affects young male participants, with symptoms beginning between 20 and 30 years of age. The diagnosis of AS after this age is not taken into consideration because the clinical onset > 50 years of age is uncommon. As a result, the identification of other inflammatory rheumatic illnesses in the elderly, such as polymyalgia rheumatica and rheumatoid arthritis, leads to the diagnosis of late-onset AS. The underdiagnosis of the disorder in this age range may be due to changes in the clinical or radiological manifestations of late-onset AS and/or spondyloarthropathy.[27]

We also found more patients had a family history of AS and positive HLA-B27, the delayed diagnosis was shorter. As we know a family history of AS is an additional risk factor for developing the disease. For example, about a 20% increased chance of developing AS was observed in those who inherit HLA-B27 and have a parent with AS.[28] However, in this case, and in our study, having a family history resulted in an earlier diagnosis of AS. The same as in the study Dincer et al showed that patients with a family history of AS had a shorter diagnostic delay.[24] In other studies, by Aggarwal and Malaviya,[29] and Seo et al,[12] a family history were not related to DD.

A cohort study by van Lunteren et al, have shown that a positive family history of AS can be used to identify patients who are more likely to be HLA-B27 positive and therefore may have an increased risk of axial spondyloarthritis.[30] It was suggested that HLA-B27 is one of the best choices for the early diagnosis of AS. However, HLA-B27 positivity is not part of the modified New York criteria for AS diagnosis, but Feldtkeller et al[31] showed HLAB27 had high sensitivity and specificity for the diagnosis of AS. The average delay was reportedly longer in HLA-B27-negative patients than in HLA-B27-positive patients, thus it is recommended to use the new ASAS classification criteria for axial SpA including HLA-B27 status for the early diagnosis of AS.[32] We also found that the average DD of the patients having HLA-B27 positive was shorter than those having HLA-B27 negative. This may be reflecting that positive HLA-B27 status may diminish the average diagnosis time and also DD.[24]

There are several limitations to this study, retrospectively collected information from patients' history about the age and first onset symptoms. But some of them did not completely remember. Although patients may have had initial symptoms before that, they did not care. Also, the small number of patients coming to the rheumatology department hospital due to lack of proper treatment and the spread of coronavirus.

6. Conclusion

General practitioners and orthopaedics were the consulted specialists and caused an average DD of more than six years. frequently lack awareness of extra-articular features and struggle to distinguish inflammatory-type back pain from other types of back pain. As a result, patients may not receive the proper care or be referred to rheumatologists. A prior diagnosis was found by multivariate analysis. HLA-B27, age, occupation, and family history are the determinants of delayed diagnosis in Sulaymaniyah patients with AS. Inflammatory back pain, one of the initial symptoms at the onset of disease, was an independent factor associated with diagnostic delay. Priority should be given to early diagnosis and prompt treatment implementation to improve the prognosis for AS patients.

Authors' Contributions

RRM concepted and designed the study. LJM executed of data, analysed, interpreted data, and drafted the manuscript. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors read and approved the final version of the article.

Conflict of Interest Disclosures

No potential conflict of interest relevant to this article was reported.

Ethical Approval

The Kurdistan Board of Medical Specialties Research Protocol Ethics Committee approved all procedures involving human subjects in this study, which was carried out by the Declaration of Helsinki's principles (Ethics Number: 727). All subjects provided their written, informed consent.

Research Highlights

What Is Already Known?

AS is a chronic, progressive, and disabling disease among rheumatological diseases.

What Does This Study Add?

- The average time lag between the onset of the first symptoms at diagnosis and the final diagnosis of AS was 6.48 years
- There were significant differences in HLAB27, age, age at diagnosis, education level, occupation, first specialist, and family history are the factors that affect delayed diagnosis in Sulaymaniyah patients with AS.
- A statistically significant positive correlation was detected between the DD and age, age at diagnosis

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