Research Article

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Diagnostic Delay in Patients with Axial Spondyloarthritis, Review of Clinical and Radiological Data: United Arab Emirates (UAE) Experience

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Abstract

Spondylarthritis (SpA) is a chronic inflammatory disease characterized by inflammation of the sacroiliac joints and spine, peripheral arthritis, enthesitis, and dactylitis. SpA can manifest mainly as axial SpA (axSpA) or peripheral SpA. AxSpA is divided into radiographic axial spondylarthritis (r-axSpA) and non-radiographic axial spondylarthritis (nr-axSpA). The main symptom of axial spondylarthritis, chronic low back pain, often occurs before the development of sacroiliitis seen on radiographs, and this delay can persist for many years. People with ankylosing spondylitis (AS), who have r-axSpA, tend to experience symptoms for at least a decade before being diagnosed. The late diagnosis of ankylosing spondylitis (AS) is a major challenge in improving patient care.

Objective: To determine the diagnostic delay and to evaluate clinical and radiological features of r-axSpA and nr-axSpA in rheumatology clinics.

Methods: Retrospective analysis of electronic medical records was performed. Patients were classified into two subgroups: r-axSpA and nr-axSpA. The time from the onset of back pain symptoms until the diagnosis of axSpA was defined as the diagnostic delay. Patient characteristics, clinical manifestations, laboratory, and diagnostic imaging results were also compared between subgroups.

Results: A total of 162 patients who fulfilled the ASAS classification criteria for axial SpA were included in the study. 65% of the patients were male, with the age group below 40 years, encompassing 50.6% of the total sample. Patients of Asian origin account for 37.7% of the population, and Emiratis comprise 22.8% of the cohort. The mean delay from symptom onset to diagnosis was an average of 4.67 years before receiving a formal diagnosis by a rheumatologist, as indicated by a standard deviation of 4.35. Of all the patients, 54.9% tested positive for HLAB27, whereas 42.6% were HLAB27 negative.

Conclusion: The mean delay from symptom onset to diagnosis was an average of 4.67 years before receiving a formal diagnosis by a rheumatologist. The time it takes for a diagnosis of axial spondyloarthropathy to be made is significantly less than for the group of patients in the real world.

Keywords: Ankylosing spondylitis • Non-radiographic axial spondylarthritis • Radiographic axial spondylarthritis • Anti-TNF • Diagnostic delay

Introduction

Delay in diagnosing spondyloarthropathies has been a recognised challenge in clinical practice [1,2]. Although recent studies suggest that this trend is improving, no current data is available for the United Arab Emirates. Axial SpA (axSpA) is a chronic inflammatory disease characterised by inflammation of the sacroiliac joints and spine, peripheral arthritis, enthesitis, dactylitis with extra-skeletal manifestations, including acute anterior uveitis, inflammatory bowel disease and psoriasis [1,2]. Its prevalence in the Middle East is lower compared to

Europe and North America [3]. However, data on prevalence in individual countries in the Middle East is still limited [4]. Patients with SpA can be distinguished according to their clinical presentation as patients with predominantly axial SpA or with predominantly peripheral SpA [3]. New Assessment of Spondylarthritis International Society (ASAS) classification criteria are currently used to classify patients with inflammatory back pain into radiographic (r-axSpA) and non-radiographic axial SpA (nr-axSpA) [5,6]. The diagnosis of axSpA remains challenging due to the often-insidious onset of this condition, with initial presentation not always being immediately apparent as an inflammatory back pain. Furthermore, although chronic back pain (CBP) lasting longer than three months is a key characteristic of axSpA, It frequently occurs in many patients with non-inflammatory back pain [7]. In SpA, genetics strongly correlate with the development of symptoms, with HLAB27 prevalence being higher than in the normal population [8]. Interestingly, data emerging from the Middle East show a lower prevalence (25%-75%) compared to Europe or North America, where the percentage exceeds 90% [9]. A meta-analysis of 64 studies in axSpA patients reported a pooled mean diagnostic delay of 6.7 years [10]. Diagnostic delay is a significant challenge in axial spondylarthritis (axSpA), with an extended interval of 8-10 years in Europe and 14 years in the United States between symptom onset and disease diagnosis [11,12]. This delay has been attributed to different factors, including the delay in seeking medical advice by the patient, socioeconomic status, and the referral system, which have contributed to the delay in diagnosis [11,13]. Delayed diagnosis in axSpA is associated with worse clinical, humanistic, and economic outcomes [14]. At the same time, treatment with TNF inhibitors improves clinical outcomes and radiographic progression more effectively when commenced earlier in the disease process [15]. 5-10% of nr-axSpA patients have been shown to develop axSpA within two years, and 20% of them within five years [16]. To our knowledge, few studies have been done to assess the delay in diagnosis in the United Arab Emirates, with few publications emerging from Saudi Arabia [17]. Our study is a cross-sectional analysis aiming to assess the delay in diagnosis in axSpA patients and its relation to demographic characteristics, HLAB27 prevalence, systemic manifestations, and axial vs non-axial involvement among UAE patients.

Material and Methods

The primary objective of this study was to estimate the diagnostic delay and to evaluate clinical characteristics of r-axSpA and nr-axSpA among patients with back pain symptoms seen in rheumatology clinics in the UAE. A secondary objective was to estimate the prevalence of HLA B 27 in patients with axSpA. Retrospective data from July 1, 2013, to June 30, 2023, with ICD 9 codes and ICD 10 codes for Ankylosing spondylitis (AS) and sacroiliitis were collected from electronic medical records (EMR) of patients seen in our rheumatology clinics. Clinical histories and radiologic data were evaluated to determine who fulfilled the ASAS classification criteria for axial SpA. AS patients who met the Assessment of Spondylarthritis International Society (ASAS) classification criteria for axial SpA were included in the study [5]. Patient characteristics such as Age, gender, nationality, time to diagnosis defined as the time in years since the onset of axial symptoms to the diagnosis of r-axSpA and nr-axSpA by a physician, radiographic data at the time of presentation, HLA B 27 positivity status, and treatment modalities were reviewed and compared between the two subgroups. Extra-articular manifestations, including uveitis and inflammatory bowel disease, or the presence or absence of peripheral arthritis at diagnosis, were noted in detail. All patients over 16 years of age who fulfil the ASAS criteria either by clinical or radiologic arms and seen in our rheumatology clinics were included in the study. Patients who don't fulfil ASAS classification criteria for axial SpA, patients who have peripheral SpA without axial SpA, patients who are missing relevant medical records and those with a history of psoriasis were excluded from the analysis. The statistical analysis was run using SPSS v.29 software. Data is presented as standard deviation and means for continuous variables and percentages for categorical and nominal variables. $\psi 2$ was used to assess the association between nominal and absolute values and the student test for continuous variables. The Pearson correlation test assessed the linear correlation in paired data sets. A p-value<0.05 was statistically significant.

Results

Demographics

A total of 162 patients who fulfilled the ASAS classification criteria for axial SpA were included in the study. Within our study cohort, a noteworthy demographic composition emerged specifically, 65% of the patients identified as male. Most patients were below the age group of 40, encompassing 50.6% of the total sample. Furthermore, it is significant to note that the preeminent ethnic groups represented were of Asian origin, accounting for 37.7% of the population, and Emiratis, comprising 22.8% of the cohort [Table 1]. 47.8% of patients were referred as established cases of axial spondyloarthropathy, and 52.2% of patients were referred with symptoms that lead to diagnosis of axial spondyloarthropathy. Furthermore, the distribution

Table 1: Demographic characteristics.

		N	Percentage
Gender	Male	106	65.4%
	Female	56	34.6%
Age	<=30 years	25	15.4%
	31-40 years	57	35.2%
	41-50 years	49	30.2%
	>50 years	31	19.1%
Nationality	Emirati	37	22.8%
	Arab (Non-Emirati)	56	34.6%
	Asian	61	37.7%
	Others	8	4.9%

of axial involvement revealed that 61.7% of patients exhibited radiographic axial involvement, while the remaining 38.3% manifested non-radiographic axial involvement. It is worth noting that 12 patients lacked X-ray images. MRI scans were obtained for 80.2 % of patients, demonstrating bone marrow oedema in 25.3% of cases, followed by sclerosis, which was present in 20.4% of patients. Within the cohort, 89 patients (54.9%) tested positive for HLAB27, whereas 69 individuals (42.6%) were HLAB27 negative. Additionally, HLAB27 status was not obtained for four patients (2.5%), as shown in Table 2. A significant finding emerged when examining the distribution of HLAB27 positivity among different ethnic groups, where 73.8% of individuals of Asian descent, 36.1% of Emiratis, and 50% of individuals of Arab descent (non-Emirati) tested positive for HLAB27 (p=0.002).

Time to diagnosis: Regarding the timeline associated with symptom onset and diagnosis, patients reported experiencing symptoms for an average of 4.67 years before receiving a formal diagnosis by the rheumatologist, as indicated by a standard deviation of 4.35. Interestingly, the HLAB27 positivity has not influenced an earlier diagnosis (4.34 years vs 5.04 years in the HLAB27 negative and HLAB27 positive groups). The only statistically significant finding was in the radiographic versus non-radiographic groups, where patients with non-radiographic axial SpA had a slightly shorter period from symptoms onset to diagnosis (5.47 vs 3.41 in r-axial and nr-axial, p=0.002) as shown in Table 3.

Systemic manifestations: In the context of systemic involvement, uveitis emerged as a noteworthy consideration within our cohort (19.1%). Distinct subset of 25 patients received a confirmed diagnosis of anterior uveitis following an ophthalmological evaluation, constituting 15.4% of the cohort. Additionally, a smaller percentage, 1.9% and 1.2% respectively, presented with pan-uveitis or scleritis. Remarkably, there was a notable male predominance, with a male-to-female

Table 2: HLAB27 and imaging characteristics.

		N	Percentage
Referral Source	Established Case	77	47.8%
	Back Pain	84	52.2%
Follow Up	No	75	46.3%
	Yes	87	53.7%
HLA status	Negative	69	42.6%
	Positive	89	54.9%
	Not done	4	2.5%
r-axial	r-axial	100	61.7%
	nr-axial	62	38.3%
X-ray	Negative	50	30.9%
	Positive	100	61.7%
	Not done or no available	12	7.4%
MRI (done in 80.2%)	Negative	18	11.1%
	Positive	112	69.1%
	Not done	32	19.8%

Table 3: Onset of Symptoms to diagnosis (time to diagnosis).

		N	Mean	Std. Deviation	t-value	p-value
Gender	Male	103	4.83	4.32	0.59	0.559
	Female	56	4.40	4.43		
r-axial Test	r-axial	98	5.47	4.75	3.23	0.002
	nr-axial	61	3.41	3.27		
HLA status	Negative	69	4.34	4.40	0.99	0.324
	Positive	87	5.04	4.35		

ratio of 3: 1, observed within the groups with positive eye involvement. It is noteworthy that 22 patients with eye involvement demonstrated radiographic axial SpA, accounting for 59.5%, while 9 patients with eye involvement displayed features of non-radiographic axial SpA. Notably, no statistically significant distinction was discerned between these groups (p=0.239). Further analysis indicated a higher prevalence of eye disease in the HLAB27 positive group, with 25.8% of these individuals manifesting eye involvement compared to 11.6% in the HLAB27 negative group (p=0.025). 6.2% of the cohort had a history of inflammatory bowel disease, within this group 90% exhibited radiographic axial involvement in contrast to the 10% who did not manifest radiographic axial involvement (p=0.09).

Imaging

It became evident that males exhibited a higher prevalence of radiographic axial involvement than females, with percentages of 70.8% and 44.6%, respectively (p=0.001). Moreover, patients who tested positive for HLAB27 were more likely to demonstrate radiographic axial involvement, as evidenced by a prevalence of 70.8% in this group compared to 53.6% among HLAB27-negative patients (p=0.026), as shown in Table 4. The utilization of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was prevalent

Table 4: Systemic manifestation in r-axial and nr-axial SpA.

		r-axial test				
		r-axial		nr-axial		
		Count	Percentage	Count	Percentage	p-value
Gender	Male	75	70.8%	31	29.2%	0.001
	Female	25	44.6%	31	55.4%	
Eye disease	No	78	59.5%	53	40.5%	0.239
	Yes	22	71.0%	9	29.0%	
HLA status	Negative	37	53.6%	32	46.4%	0.026
	Positive	63	70.8%	26	29.2%	
IBD	No	91	59.9%	61	40.1%	
	Yes	9	90.0%	1	10.0%	0.09

among our cohort, with an overwhelming majority of 79% of patients reporting their usage at the time of enrolment. Disease-modifying anti-rheumatic Drugs (DMARDs), including sulfasalazine and Methotrexate, were administered in 39% of cases and 9.9% of cases, respectively. A noteworthy observation was the substantial proportion of patients, amounting to 73.5%, who received treatment with biologic therapies, underscoring the prominence of this therapeutic modality. Conversely, a smaller percentage of the cohort, comprising 22.2%, had not been exposed to any form of biologic intervention.

Discussion

Our study aimed to characterise the delay in diagnosis of SpA and identify potential reasons for this delay. In our study, 52.2% were newly diagnosed cases, while the remaining 47.8% had already established axial spondyloarthropathy diagnosis. Whilst our study was not able to identify the primary source of diagnosis in the established cases which were already diagnosed, Deodhar A et al. have stated that only (37 %) were referred to and diagnosed by rheumatologists; the others were diagnosed in primary care (25.7 %), chiropractic/ physical therapy (7 %), orthopaedic surgery (3.8 %), pain clinic (3.6 %), acute care (3.4 %), and other (19.2 %) settings [12]. The median time from back pain diagnosis to a rheumatology referral was 307 days, and from the first rheumatologist visit to AS diagnosis, it was 28 days [12]. Regarding the timeline associated with symptom onset and diagnosis, patients reported experiencing symptoms for an average of 4.67 years before receiving a formal diagnosis by a rheumatologist. This is shorter compared to other reported studies. Vedat G et al. stated that the mean diagnostic delay was 8.1 ± 8.6 years in all patients with AS [18]. The mean time from symptom onset to the correct diagnosis was 9.7 ± 9.3 years. Only 4% (n = 16) of patients presented to rheumatologists for the first visit for back pain, whereas 30% (n = 118) consulted a physiatrist, 25% (n = 99) an orthopaedic surgeon, and 16% (n = 63) a neurosurgeon. Lumbar disc hernia (LDH) was the most reported initial diagnosis for about 33% of patients, and prior diagnosis of LDH was a predictive factor for diagnostic delay [18]. Before the introduction of the Assessment of Spondylarthritis International Society criteria in 2009 [5], diagnosis and classification of axSpA relied heavily on the presence of X-ray changes in the SI joints or spine, and therefore, patients with early disease were missed. Including MRI of the SI joints in the diagnostic approach in patients with suspected axSpA allows for disease recognition during the initial stages of the disease [19]. Our results show that despite the increased access to MRI, 19.8% of diagnosed patients did not have an MRI done, while 7.4% had no X-rays or data was unavailable. SpA is associated with the major histocompatibility complex (MHC) class I human leucocyte antigen-B27 (HLA-B27) [20,21]. The approximate prevalence of HLA-B27 among the general population in the United States is 6%; in Europe, it is 4-14%, with a higher percentage in northern Europe; and in China, the prevalence is 8% [21,22]. HLA-B27 is present in about 85-95% of patients with AS in the US, Europe and China. However, within a population, only 5% of HLA-B27-positive individuals develop AS or another form of SpA [23]. In our study, 54.9% tested positive for HLAB27. Of these, HLAB27 was positive in 70.8% of patients with r-axSpA compared to 29.2% with nr-axSpA. HLA-B27 was positive in 76% of AS patients but only 36% in the 'other SpA' cohort in a study of UAE population by Quraishi MK et al. [24]. In our study, HLAB27 positivity has not influenced an earlier diagnosis (4.34 years vs 5.04 years in the HLAB27 negative and HLAB27 positive groups). The only statistically significant finding was in the radiographic versus non-radiographic groups, where patients with non-radiographic axial SpA had a slightly shorter period from symptom onset to diagnosis (5.47

vs 3.41 in r-axial and nr-axial). Bedaiwi et al, reported the delay in diagnosis of AS to be 6.69 ± 5.83 years. Patients with non-radiographic axial SpA and those with AS were more likely to be HLA-B27-positive (66.67% and 61.22%, respectively). There was no statistically significant relationship between HLA-B27 positivity and the delay of diagnosis or age at diagnosis [17]. Uveitis was present in 19.1% within our cohort, while 6.2% had a history of inflammatory bowel disease. Al Attia et al, reported a much higher occurrence of uveitis in Arab and lower occurrence in South Asian (Indian Subcontinent) population in AS patients [25]. In our study, the duration of the delay to diagnosis was less in comparison to male patients, although not statistically significant—furthermore, 65% of the patients identified as male in our cohort. Most patients were below the age group of 40 years, encompassing 50.6% of the total sample. Imkeredeker et al, showed that factors associated with diagnostic delay, HLA-B27 negativity, female sex, younger age at symptom onset and psoriasis were factors independently associated with a longer diagnostic delay in patients with axSpA [26]. The duration of the delay to diagnosis is further lower in females, possibly since females are accessing health care earlier and males are busy with work, as the majority are ex-pats and are the primary workforce. This is somewhat contrary to other published data that shows that women usually experience a longer delay in diagnosis compared to men [27]. Non-radiographic axial SpA had a shorter duration to diagnosis as a consequence, probably related to more accessible access to obtain MRI in our cohort of patients. To our knowledge, this is the first observational study looking at the delay in SpA diagnosis in the UAE. Our study had a few limitations, and these were probably related to subjective bias from patients recalling the exact date of symptom onset and to the relatively small number of patients.

Conclusions

The mean delay from symptom onset and diagnosis was an average of 4.67 years before receiving a formal diagnosis by a rheumatologist, as indicated by a standard deviation of 4.35. The time it takes to diagnose axSpA is significantly less than that of the group of patients in the real world. This could be due to easy accessibility to healthcare in the United Arab Emirates (UAE), education of the primary care physicians and early referral to the rheumatology clinic. Establishing local registries will allow the collection of more data regarding the delay in diagnosis. Hopefully, this will lead to the generation of strategies adapted to the local environment that will allow further interventions to reduce this delay.

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