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ORIGINAL ARTICLE

Prevalence of HLA-B27 in the general population and in patients with axial spondyloarthritis in Saudi Arabia

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Abstract The prevalence of HLA-B27 in the general population and in axial spondyloarthritis (axSpA) patients in Saudi Arabia is unknown. The aim of this study was to evaluate the prevalence of HLA-B27 in these two populations and describe the delay in diagnosis of axSpA patients. The prevalence of HLA-B27 in the general population was evaluated using cord blood and healthy organ transplant donor databases. Data from patients with axSpA were collected retrospectively from five centers. Ankylosing spondylitis (AS) was diagnosed based on a positive X-ray, as evaluated by two independent readers. Patients with inflammatory bowel disease and psoriasis were excluded. A total of 134 axSpA patients were included, of whom 107 (79.9%) had AS, and most (67.2%) were males. HLA-B27 was positive in 60.4, 69, and 25.9% of patients with axSpA, AS, and non-radiographic axSpA (nr-axSpA), respectively. The median and interquartile range (IQR) ages at symptom onset and disease diagnosis were 26 (20–33) and 30 (25–38) years, respectively. The median delay to diagnosis was 3 (1–6) years. There was a negative correlation between the time of onset of symptoms and the delay in diagnosis ($r = -0.587$). Male gender and HLA-B27 positivity were associated with a younger age at symptom onset/diagnosis ($p < 0.05$). HLA-B27 was positive in 82/3332 (2.5%) and 27/1164 (2.3%) individuals in the cord blood and healthy organ transplant donor databases, respectively. The prevalence of HLA-B27 is lower in the general Saudi population and in axSpA patients compared to Caucasians, thus, limiting its utility as a diagnostic criterion.

Keywords Delayed diagnosis · HLA-B27 · Prevalence · Spondyloarthritis

Introduction

The spondylarthropathies (SpA) are a group of diseases that share many clinical features, pathogenic pathways, and a common genetic predisposing background. Ankylosing spondylitis (AS) is considered the prototype disease and exhibits predominantly axial involvement. The association between the

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histocompatibility antigen HLA-B27 and AS has been known for over 40 years [1, 2]. This strong association is most prominent in Caucasians, with a prevalence of HLA-B27 in AS patients reaching 90–95%. This fact has led to the incorporation of HLA-B27 into the Assessment of SpondyloArthritis International Society (ASAS) classification criteria and the development of a clinical arm that relies heavily on HLA-B27 positivity [3]. However, the prevalence of HLA-B27 in the general population varies significantly between ethnicities, ranging from almost nil in Australian Aborigines to 50% in Haida Indians [4]. In Arabs, the prevalence of HLA-B27 in the general population and in axial SpA (axSpA) patients is lower than that in Caucasians, but again, this varies depending on the country and origin of the study population [5–9]. The prevalence of HLA-B27 in Saudi Arabia is unknown. Thus, the aim of this study was to investigate this prevalence in both the general population and in patients with axSpA.

Methods

This study consisted of two essential parts:

1- Evaluation of the prevalence of HLA-B27 in the general population, which was assessed by examining the HLA type of cord blood donors and healthy live donors for organ transplantation in the Department of Pathology and Laboratory Medicine at King Faisal Specialist Hospital and Research Center (KFSH & RC). The HLA type of patients, cord blood samples, and consecutive healthy donors was determined with the DNA molecular typing method using reverse sequence specific oligonucleotide probes (rSSOP) according to the manufacturer's instructions (One Lambda, Canoga Park, CA, USA and/or Immucor, Stamford, CT, USA).

2- Evaluation of the prevalence of HLA-B27 in a population of patients with AS and non-radiographic axSpA (nr-axSpA) from five different institutions, including KFSH & RC, King Khalid University Hospital (KKUH), Security Forces Hospital (SFH), Hera General Hospital, and King Fahad Hospital-Jeddah (KFHJ) between the period 1990 and 2016. Information was collected through a standardized data collection sheet. Patients' demographics, HLA-B27 positivity, extra-articular manifestations, and use of biologics were recorded. The inclusion criteria consisted of an age of onset ≥18 years, Saudi nationality, and confirmed diagnosis of axSpA by a certified rheumatologist. All patients had sacroiliitis diagnosed by X-ray and/or magnetic resonance imaging (MRI). Radiographs of the sacroiliac joints were reviewed by two independent reviewers (one rheumatologist and one radiologist). Disagreements were resolved by consensus or a third party (KI), if needed. Patients with missing radiology or HLA-B27 data, pediatric axSpA, confirmed diagnosis of psoriasis (Ps) or inflammatory bowel disease (IBD) were excluded. Institutional ethical approval was obtained at all participating sites.

Statistical analysis

Descriptive statistics were used to report demographics. Due to the skewness of the data, non-parametric statistics were used to compare patient subgroups. The association between the delay in diagnosis and year of symptom onset was assessed by Spearman's correlation coefficient. The analyses were performed using the SPSS 21 statistical software package.

Results

AxSpA population

A total of 183 axSpA patients were recruited, of whom 134 were included in the final analysis (Fig. 1). The number of cases identified was increasing over time (Fig. 2). There was a male predominance of 67.2%. Twenty-six (19.4%) patients had at least one extra-articular manifestation. The majority of the cohort were recruited from the central region of Saudi Arabia (45.5%), followed by the southern (23.9%) and western regions (17.95). The eastern and northern regions had the lowest numbers (7.5 and 5.2%), respectively. The median and interquartile range (IQR) ages at symptom onset and disease diagnosis were 26 (20–33) and 30 (25–38) years, respectively (Table 1). The median (IQR) diagnosis delay was 3 (1–6) years. HLA-B27 was positive in 60.4, 69, and 25.9% of patients with axSpA, AS, and nr-axSpA, respectively. The prevalence of HLA-B27 positivity was higher in males than that in females (76.7 vs 23.7%; $p < 0.001$) and higher in AS patients than that in nr-axSpA patients (69 vs 25.9%; $p < 0.001$) (Table 2).

Male gender and HLA-B27 positivity were associated with a younger age at symptom onset/diagnosis ($p < 0.05$), but no significant difference was observed in diagnosis delay. The median (IQR) delay was 4 (1–7) years for HLA-B27-positive patients versus 2 (1–6) years for HLA-B27-negative patients ($p = 0.186$). The use of biologics was documented in 121 (90.3%) of patients. Most of them (62.7%) were on their first biologic. HLA-B27-positive patients were more likely to be on biologics ($p = 0.037$), with no difference in the median number of biologics used.

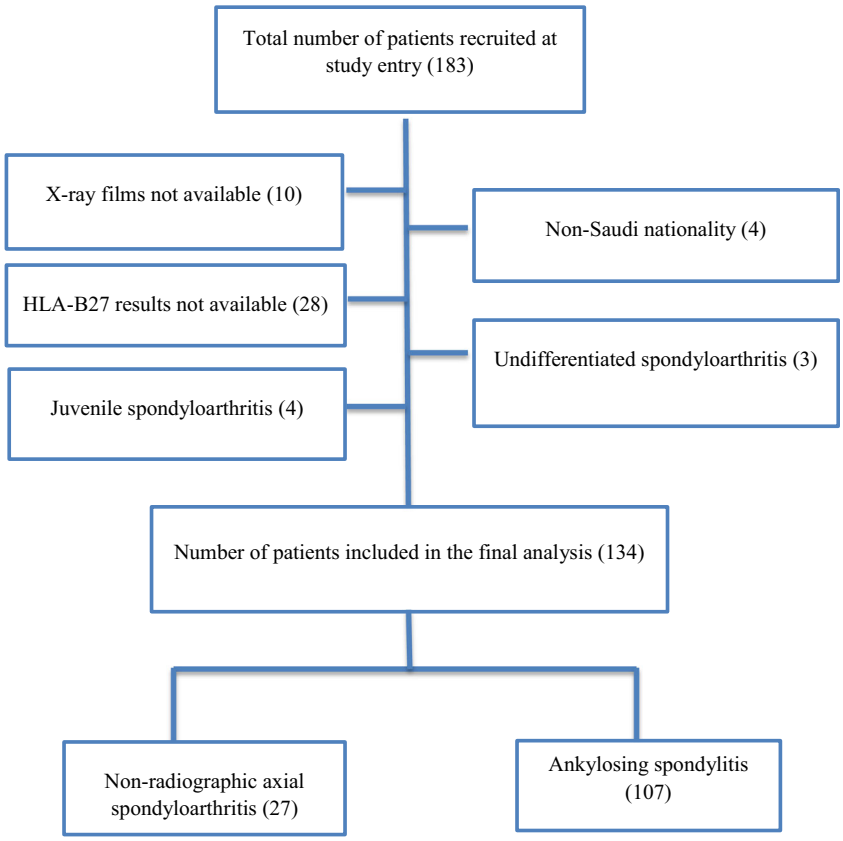

Fig. 1 Flow chart of the patient population studied

There was a negative correlation between the year of symptom onset and the delay in diagnosis ($r = -0.587$) (Fig. 3). Twenty-three patients (17.2%) were diagnosed within a year of symptom onset. Of those, 15 (65.2%) were diagnosed in

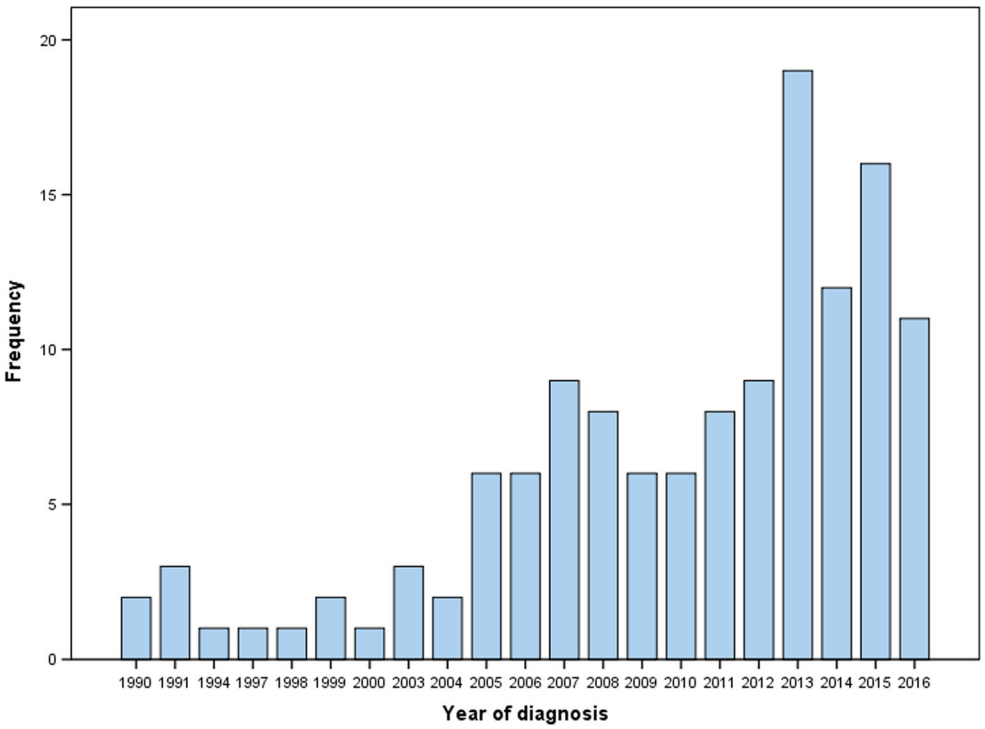

Fig. 2 Distribution of axial spondyloarthritis patients diagnosed between 1990 and 2016

Table 1 Demographic characteristics of the patient population. Interquartile range (IQR)

Study population	*N* = 134
Male gender	90 (67.2%)
Ankylosing spondylitis	107 (79.9%)
Age at symptom onset	26 (IQR 13) years
Age at diagnosis	30 (IQR 13) years
Delay in diagnosis	3 (IQR 5) years
Presence of extra-articular manifestations	26 (19.4%)
Patients started on biologics	121 (90.3%)
Number of biologic(s) used	
0	13 (9.7%)
1	84 (62.7%)
2	26 (19.4%)
3	11 (8.2%)
Region	
Central	61 (45.5%)
Southern	32 (23.9%)
Western	24 (17.9%)
Eastern	10 (7.5%)
Northern	7 (5.2%)

2009 and beyond. Eighteen (14%) patients reported symptom onset after the age of 40 years (Fig. 4).

General population

HLA-B27 was positive in 82/3332 (2.5%) and 27/1164 (2.3%) individuals from the cord blood and healthy organ transplant donor databases, respectively, with an overall mean prevalence of 2.4% (Table 2).

Table 2 Prevalence of HLA-B27 in various populations

Population	Number (%)
Saudi population	
Entire cohort	109/4496 (2.4)
Cord blood bank	82/3332 (2.5)
Healthy organ transplant donor databases	27/1164 (2.3)
Axial spondyloarthritis population	
Entire spondyloarthritis cohort	81 (60.4)
Ankylosing spondylitis	74 (69)
Non-radiographic axial spondyloarthritis	7 (25.9)
Males	69 (76.7)
Females	12 (27.3)
Patients with extra-articular manifestations	18 (69.2)
Patients without extra-articular manifestations	63 (58.3)

Discussion

HLA-B27 in the general population

Determining the prevalence of HLA-B27 in the general population and in SpA patients is crucial to evaluate its diagnostic utility in evaluating patients with low back pain. The Saudi population is multiethnic and is composed of individuals with various backgrounds, including major Arabian tribes, Asian and African ancestries. Studies evaluating the prevalence of HLA-B27 in various Arab populations have shown conflicting results. Al-Attia et al. reported an overall HLA-B27 prevalence in the U.A.E of 6.4%. When isolating Arabs in the analysis, the frequency of positivity was 5.7% in Arabs versus 7.4% in Asians. Upon further dissection of different Arab subgroups, Emirian Arabs showed a low prevalence of 0.5% compared to the Yemeni population, in which the prevalence reached 17% [5]. Similar to our findings, Mustafa et al. reported the prevalence in Jordan to be 2.4% in a population that consists mainly of native Jordanians and Palestinian refugees [7]. This low prevalence in the general population may be reflected in the prevalence of SpA and the prevalence of HLA-B27 positivity in SpA patients. An important limitation of assessing HLA-B27 positivity in the current study is using healthy organ donors which could lead to selection bias. Taking this in mind, cord blood bank is more representative of the general population, as it is taken from a non-selected group of donors. The HLA-B27 positivity from the two databases is very close. This points that our results might be a reflection of the true prevalence in the Saudi population.

HLA-B27 in the SpA population

There are few data on HLA-B27 prevalence in the Arabian Peninsula and Arab populations. In a small case series, Al-Arfaj A. found that HLA-B27 was positive in 8 out of 12 AS patients (66.7%) [10]. Al-Amayreh and Zaidat reported a prevalence of 82% HLA-B27 positivity in 52 AS patients from North Jordan [11]. In a study conducted in Qatar, Abdelrahman et al. evaluated 119 AS patients of various backgrounds. Of the 66 Arabs included in the study, 49 (74%) patients were HLA B27 positive [9]. In a study from Egypt with a different patient population, Tayel et al. conducted a cross-sectional survey of all SpA patients with pure axial disease, representing 24% of the studied population and found the prevalence of HLA-B27 positivity to be 58.7% [12]. One study that pooled data from 169 SpA patients from Qatar, Saudi Arabia, Egypt, and Kuwait reported a 68.9% prevalence of HLA-B27 positivity among the 55 AS patients in the cohort [13].

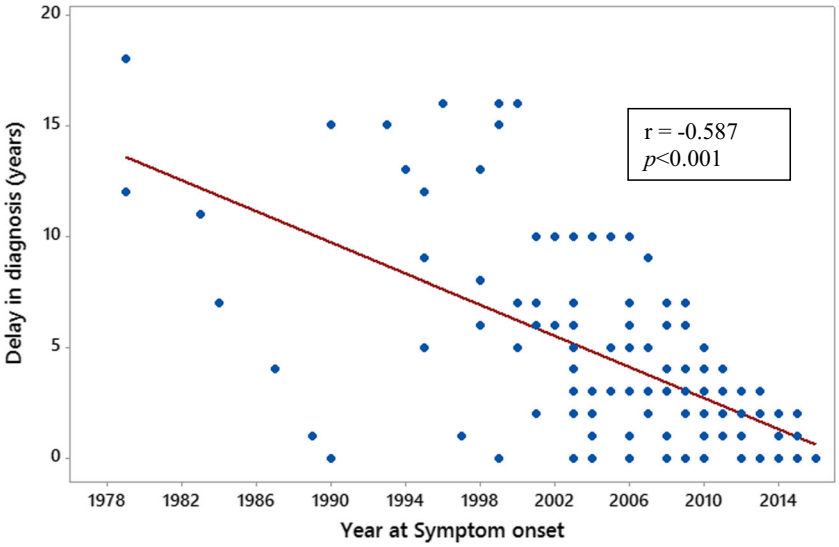

Fig. 3 Correlation between the year of symptom onset and delay in diagnosis

Diagnostic delay in axSpA

Diagnostic delay remains an important factor complicating the management of axSpA globally and in the region [14]. Despite improvements in early detection due to the modification of diagnostic criteria [3, 15] and screening algorithms [16], recent studies from the Middle East, North Africa, and Asia Pacific regions have continued to report a mean delay ranging from 4 to 7 years depending on the population studied and definition used. Data from Morocco described by Ibn Yacoub et al. reported that the mean delay in the diagnosis of AS was 4.12 ± 3.99 years [17]. Dincer et al. reported a longer mean diagnosis delay of 6.05 ± 5.08 years in Turkish patients [18], and similar results were published in studies from India and Korea [19, 20].

In our study, we found a significant delay in the diagnosis of axSpA patients, similar to what has been previously reported. This delay has not diminished over the last decade, possibly because there are many patients with symptom onset dating back more than 10 years who were recently diagnosed. Factors identified in the literature that could play a role in this diagnosis gap include gender, HLA-B27 negativity [18], period of diagnosis [21], underlying structural lesion prior to SpA diagnosis, absence of SpA in first-degree relatives [18], and absence of peripheral symptoms [21]. Such factors were not evaluated in the current study but would be important to assess in a future prospective cohort. Diagnostic delay translates to a delay in management, which has a negative impact on patients' quality of life, the disease course, and response to therapy [22]. One interesting finding in our cohort is the percentage of patients who had symptom onset after the age of 40, which is considered the cutoff age in the ASAS classification criteria for inflammatory back pain [23]. As a result, this group of patients could be missed when adapting screening algorithms developed in the Caucasian population.

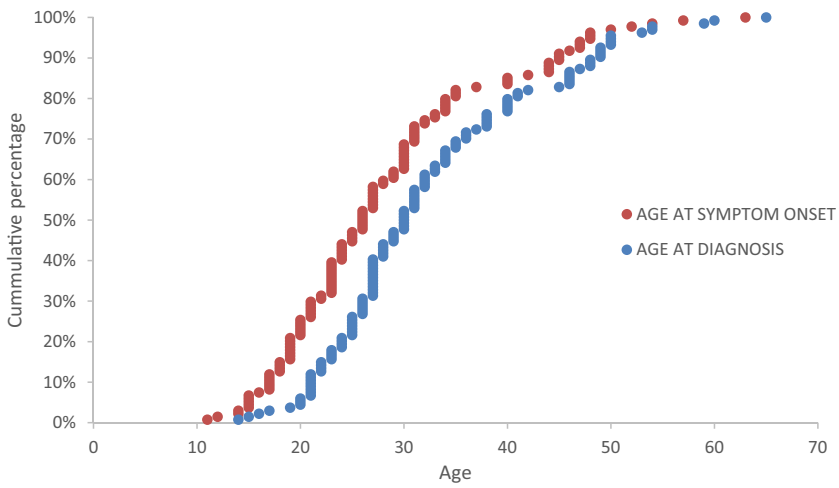

Fig. 4 Cumulative distribution of age at symptom onset and age at diagnosis

Use of biologics in axSpA

Access to biologics in our patient population was high, because care is provided to all Saudi Arabian citizens by the government through a national health care system that covers all costs, including medications. However, the current model may not be able to meet the high economic burden caused by the increase in newly diagnosed patients demonstrated in our study, which should be considered in the implementation of the cooperative health insurance scheme in Saudi Arabia.

Limitations of our study include selection bias, as most of the patients included were from tertiary care centers. We also did not evaluate factors associated with diagnostic delay or use of biologics due to the retrospective nature of our study.

In conclusion, the prevalence of HLA-B27 in the general population and in patients with axSpA is lower than that reported in Caucasians, thus, limiting its sensitivity as a diagnostic criterion. Our study also highlights the significant delay in the diagnosis of axSpA. There is an urgent need to develop a prospective nationwide cohort to analyze causes of diagnostic delay and unmet needs in the management of SpA patients in Saudi Arabia.

Compliance with ethical standards

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Disclosures None.

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