



The treatment journey for patients with axial spondyloarthritis in North Africa and the Middle East: From diagnosis to management

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Abstract

The management of axial spondyloarthritis (axSpA) is challenging worldwide, and the particular challenges shared by North Africa and the Middle East are mainly related to early diagnosis and standardized management. We believe there are several reasons for these challenges, including: (a) limited awareness of the disease manifestations and prevalence in the region among physicians; (b) the concept of nonradiographic axSpA, while accepted with some difficulty by the rheumatology community, may not be well understood by the referring primary care physicians; (c) access to, and training in magnetic resonance imaging varies greatly between countries in the North Africa and Middle East region, and this may have a large impact on early diagnosis; (d) country-specific treatment guidelines are unavailable; and (e) economic and cultural factors influence patients' attempts to seek and continue treatment. In this review, we will discuss the prevalence of axSpA in North Africa and the Middle East, as well as the challenges to diagnose and treat patients in this region. As rheumatologists practicing in North Africa and the Middle East, we also provide suggestions to assist physicians, other healthcare professionals, and researchers in facilitating early, accurate diagnosis and treatment of axSpA.

KEYWORDS

axial spondyloarthritis, diagnosis, management, Middle East, North Africa, treatment

1 | INTRODUCTION

Spondyloarthritis (SpA) comprises a spectrum of chronic inflammatory conditions that share common clinical features, laboratory abnormalities, and imaging features, and genetically tend to be associated with human leukocyte antigen B27 (HLA-B27).¹ The spectrum includes radiographic axial SpA (axSpA, known as ankylosing spondylitis [AS]), nonradiographic axSpA (nr-axSpA), psoriatic arthritis, inflammatory bowel disease-related arthritis, reactive

arthritis, and undifferentiated SpA.^{1,2} The onset of symptoms tends to occur at a relatively young age, often when patients are in their 20s.¹ The reported age at the time of initial symptom presentation in North Africa and the Middle East, including Saudi Arabia, Qatar, United Arab Emirates, Kuwait, and Egypt ranges between 23 and 32 years.³⁻⁷

AxSpA primarily involves the sacroiliac joints and/or spine.¹ Establishing a diagnosis of axSpA, particularly at an early stage in the disease, can be challenging.⁸ In 2009, the Assessment

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of SpondyloArthritis international Society (ASAS) introduced classification criteria to minimize the lag time between symptom onset and diagnosis in patients with nr-axSpA.² The classification includes 3 main domains: clinical (chronic back pain and SpA features, including elevated C-reactive protein), imaging (X-ray and magnetic resonance imaging [MRI]), and HLA-B27 positivity.² In this classification, patients with a 3-month or longer history of chronic back pain starting before 45 years of age are classified as having axSpA if sacroiliitis is evident on X-ray (bilateral \geq grade 2 or unilateral grade 3 or 4 based on the modified New York criteria for AS⁹) or inflammation highly suggestive of sacroiliitis on MRI, plus at least 1 SpA feature; or if they are positive for HLA-B27 and have at least 2 other SpA features.

Patients who do not have sacroiliitis evident on X-ray but who still meet the ASAS criteria for axSpA are considered to have nr-axSpA.² Since inflammation can be detected on MRI earlier in the disease course than sacroiliitis is visible on X-ray, it was expected that MRI would decrease the lag time between symptom onset and diagnosis, which has typically been reported to be 8-10 years.¹⁰ While the lag time varies between studies, study results indicate that it is still considerable in Europe as well as in North Africa and the Middle East. Pooled data from studies conducted in Paris, France in 2009 and 2013 found the median diagnostic delay to be 2 years (interquartile range [IQR] 1-7 years) and the mean to be 4.9 (standard deviation [SD] 6.3) years.¹¹ A study conducted in the UK in patients who were diagnosed with axSpA between 2009 and 2013 reported the mean (SD) delay to be 8.5 (9.0) years and the median (IQR) to be 5.0 (2-12 years).¹⁰ Studies across North Africa and the Middle East have reported the delay to be in the range of 2.5-6 years.^{4,5,7,12}

The reason for the delay in diagnosis is likely multifactorial. We believe possible explanations include the following: (a) misperception as to whether the ASAS criteria are for diagnosis or classification in clinical practice; (b) additional classification criteria may need to be added to the ASAS guidelines; (c) lack of awareness about axSpA among primary care physicians; (d) limited knowledge of the ASAS criteria among radiologists; (e) limited awareness of nr-axSpA among rheumatologists; (f) low reimbursement and/or access to MRI in some countries; and (g) poor specificity of the main symptom of low back pain, its high response to nonsteroidal anti-inflammatory drugs (NSAIDs), and the intermittent pattern in the early phases of the disease. Despite these challenges, it is important to diagnose axSpA early in the disease course and provide effective treatment in order to maintain favorable health-related quality of life for patients and possibly limit progression of the disease.¹

International guidelines have been developed to assist clinicians in the management of axSpA.^{13,14} The guidelines by Smolen et al. recommend that patients achieve a treatment target of clinical remission or inactive disease, defined as having no significant disease activity based on clinical and laboratory measurements.¹³ These guidelines also state that imaging results may also be used to monitor disease activity.¹³ Once the treatment target is achieved, disease activity should be monitored regularly and therapy adjusted as needed to maintain it.¹³

Despite having international treatment guidelines, some countries in North Africa and the Middle East face challenges in the

TABLE 1 Prevalence of axial spondyloarthritis in various countries and regions of the world

| Reference | Country/region | Prevalence (95% CI) |
|----------------------------------|---|---------------------|
| Stolwijk 2016 ^{15a} | Middle East | 0.11 (0.02-0.27) |
| | Europe | 0.25 (0.18-0.33) |
| | North America | 0.20 (0.10-0.34) |
| | South America | 0.14 (0.02-0.34) |
| | East Asia | 0.16 (0.10-0.25) |
| | South Asia | 0.06 (0.00-0.37) |
| Burgos-Varga 2016 ^{16b} | Africa (Morocco, Algeria, and South Africa) | 0.16 (0.11-0.21) |
| | Asia | 0.36 (0.32-0.41) |
| | Europe | 0.30 (0.24-0.35) |
| | Latin America | 0.19 (0.04-0.34) |

^aPrevalence of ankylosing spondylitis in the general population.

^bPrevalence of nonradiographic axial spondyloarthritis among patients with inflammatory back pain.

diagnosis and treatment of patients with axSpA.⁷ This may be the result of differences in the prevalence of the disease and of HLA-B27 positivity, as well as the structure of the particular healthcare systems in those countries.⁷ In this review, we discuss the disease burden of axSpA in North Africa and the Middle East, and the challenges that rheumatologists face regarding early detection and ongoing management of axSpA. We also provide insights into how these challenges may be addressed.

2 | PREVALENCE OF axSpA IN NORTH AFRICA AND THE MIDDLE EAST

The prevalence of axSpA in the Middle East has been reported to be lower than in Europe, North America, South America, and East Asia, and slightly higher than in South Asia, although all of the confidence intervals overlap (Table 1).¹⁵ A study conducted in 19 countries that evaluated the occurrence of nr-axSpA among patients with inflammatory back pain found the prevalence in Africa (based on data from Morocco, Algeria, and South Africa) to be lower than in Asia and Europe, and similar to Latin America.¹⁶ Data on the prevalence of axSpA in individual countries in North Africa and the Middle East are limited.¹² Studies have reported prevalence rates of 0.12% in Iran¹⁷ and 0.49% in Turkey.¹⁸ Prevalence data for various countries and regions of the world from 2 large studies are provided in Table 1.

3 | PREVALENCE OF HLA-B27 POSITIVITY

In North Africa and the Middle East, the prevalence of HLA-B27 reported in the general population is lower (0.3%-7%) than that reported in the United States and Europe (6%-25%).¹⁹ In addition, the



association between HLA-B27 and SpA is weaker in North Africa and the Middle East (approximately 25%-75%) than in other regions of the world (>90%) (Table 2).²⁰ However, the prevalence of HLA-B27 remains higher in patients with SpA than in the general population.¹⁹

In a global study of patients with nr-axSpA, the proportion of patients who were HLA-B27 positive was 71% in Africa (based on data from Morocco, Algeria, and South Africa), 62% in Asia, and 85% in Europe.¹⁶ Another global study found the prevalence of HLA-B27 in patients with nr-axSpA in the Middle East and South Africa to be 38%, compared with 54% in Europe and Canada, 77% in China, and 54% in Latin America.²¹ The reported prevalence of HLA-B27 positivity among patients with axSpA in various countries in North Africa and the Middle East is provided in Table 2.

4 | CHALLENGES TO EARLY DETECTION AND DIAGNOSIS

Several factors are associated with delayed diagnosis of axSpA in North Africa and the Middle East, and these can be broadly divided into physician-related, patient-related, disease-related, and health-care-related factors (Table 3).

5 | INTERNATIONAL TREATMENT GUIDELINES

In North Africa and the Middle East, 2 international guidelines commonly used in day-to-day practice for the diagnosis and management of axSpA are the ASAS-EULAR guidelines (ASAS in collaboration with the European League Against Rheumatism)²² and the ACR/SAA/SPARTAN guidelines (American College of Rheumatology in collaboration with the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network).¹⁴

Both non-pharmacological and pharmacological treatment options should be discussed with patients diagnosed with axSpA.²² Non-pharmacological management options include physiotherapy, exercise, and educating patients about axSpA and also the importance of not smoking.^{22,23} Participation in an exercise regimen may improve mobility, physical function, and pain.²³ There is consensus among the guidelines that NSAIDs are recommended as the first-line pharmacological treatment for axSpA.^{14,22} Use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, sulfasalazine, and leflunomide should be limited to patients with peripheral SpA in addition to axSpA.^{14,22}

| Reference | Country | Disease | Percentage of patients with HLA-B27 positivity |
|--------------------------------|------------------------|----------|---|
| Abdelrahman 2012 ²⁷ | Ethnic groups in Qatar | AS | All patients: 69% Arab: 74% Asian: 61% Asian Indian: 73% Qatari: 82% Jordanian/Palestinian: 72% Egyptian: 90% |
| Alam 2017 ⁵ | Qatar | AS | 81% |
| Omair 2017 ⁴ | Saudi Arabia | AS | 69% |
| | | nr-axSpA | 26% |
| Quraishi 2018 ²⁸ | United Arab Emirates | AS | 76% |
| Tayel 2012 ²⁹ | Egypt | AS | 59% |
| Ziade 2017 ¹⁹ | Algeria | AS | 69% |
| | Iraq | | 84% |
| | Iran | | 67%, 69%, 73% |
| | Israel | | 79% |
| | Jordan | | 75% |
| | Qatar | | 74% |
| | Saudi Arabia | | 67% |
| | Syria | | 60% |
| | Tunisia | | 62%, 69% |
| | Turkey | | 70%, 91% |
| | United Arab Emirates | | 56% |
| Ziade 2019 ³⁰ | Lebanon | axSpA | 41% |

TABLE 2 Prevalence of HLA-B27 positivity among patients with axSpA in North Africa and the Middle East

Abbreviations: AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; nr-axSpA, nonradiographic axial spondyloarthritis.

**TABLE 3** Challenges to early detection and diagnosis of axSpA in North Africa and the Middle East

| Physician-related factors |
|---|
| Primary care physicians sometimes have a limited knowledge of axSpA, leading to a lag time in the referral of patients with low back pain to a rheumatologist. ³¹ |
| Awareness of nr-axSpA, in particular, is low. ³¹ |
| Patients are often managed with NSAIDs |
| Patients with joint pain are often managed by orthopedic specialists. |
| Since radiographic axSpA is more prevalent in males, with the first symptoms appearing in patients in their 20s, ¹ females and patients over 45 y of age may be less likely to receive a prompt referral to a rheumatologist. |
| In some regions there is a shortage of rheumatologists, and patients may have a long wait for an appointment. ²⁴ |
| It can be challenging for rheumatologists and radiologists to interpret MRI findings suggestive of sacroiliitis, and variation among readers is common. ¹ |
| Patient-related factors |
| Patients with fewer socioeconomic resources may consult a pharmacist rather than a physician and purchase nonprescription NSAIDs to manage pain. |
| Patients may self-treat with traditional approaches, such as herbal treatments, cupping, and/or spiritual healing. ³² |
| Patients may seek care from other specialties, such as orthopedics, neurology, or neurosurgery, believing that such specialists are experts in treating back pain. |
| Patients who are not well-informed about chronic autoimmune conditions may interpret the symptoms of axSpA to be a normal part of life and only consult a physician when the disease interferes with normal daily functioning. |
| Disease-related factors |
| The association between HLA-B27 and axSpA appears to be lower among North African and Middle Eastern populations than Western populations. ¹⁹ |
| Thus, the HLA-B27 antigen test may be expensive, have limited availability, and/or prove less useful in diagnosing axSpA in this region. ^{19,20} |
| In areas where access to MRI is limited, detecting axSpA without evidence of radiographic sacroiliitis can be challenging, ⁷ and a negative HLA-B27 test result may give false reassurance for patients and physicians. |
| The tradition of arranged marriage in North Africa, especially between relatives, ³³ may potentially contribute to disease with distinct genetic characteristics. |
| Healthcare-related factors |
| In some areas, access to healthcare varies according to socioeconomic status. ⁷ |
| Insurance and/or healthcare policies may affect the speed of diagnosis of axSpA. ³¹ |
| In the private sector, self-pay patients may experience delays due to the expense of physician visits, laboratory and imaging resources, and medications. |
| General practitioners, family physicians and orthopedic surgeons may also delay referral due to fear of losing a patient (particularly in the private sector), or due to interpreting a favorable response to NSAIDs as sufficient to treat the underlying condition. |

Abbreviations: axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; nr-axSpA, nonradiographic axial spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs.

In patients with high disease activity that persists following treatment with conventional therapies, physicians should consider biologic DMARD (bDMARD) therapy.²² The current practice is to begin with a tumor necrosis factor- α (TNF) inhibitor (ie, adalimumab, certolizumab, etanercept, golimumab, or infliximab).²² If this treatment is unsuccessful, then consideration should be given to a different TNF inhibitor or to an interleukin-17 inhibitor (ie, secukinumab or ixekizumab).²²

While the ASAS-EULAR and ACR/SAA/SPARTAN guidelines recommend considering the use of bDMARDs in patients with persistently high disease activity after conventional treatments, no consideration is given to a potential “window of opportunity” during which early administration of bDMARDs could improve patient outcomes.^{14,22}

6 | CHALLENGING ASPECTS OF MANAGING axSpA IN NORTH AFRICA AND THE MIDDLE EAST

In some countries, access to treatment, and particularly to new therapies, is limited.^{20,24} Use of TNF inhibitors may be hindered due to cost restrictions and the risk of infections such as tuberculosis.^{7,20}

A number of factors contribute to the variability in the level of care within rheumatology across different countries in the region.²⁴ These include the amount of funding for healthcare provided by the government, the number of rheumatologists, the type of healthcare system (ie, public and/or private), whether or not the country is having international or internal conflicts, and

**TABLE 4** Author suggestions for improving the management of axSpA in North Africa and the Middle East**(1) Research**

- Well-designed studies across countries are needed to:
 - estimate axSpA prevalence, demographics, phenotypes, associated extra-articular manifestations and comorbidities, and determine the association with HLA-B27 and other biomarkers.
 - evaluate diagnostic markers other than HLA-B27. Some studies have evaluated a promising marker, anti-CD74 antibody.³⁴
 - evaluate treatment strategies, patient beliefs, and treatment adherence.
- Due to genetic differences across populations,³¹ clinical studies of new treatments should include patients from North Africa and the Middle East.
 - Relatively few studies have been published from these regions.^{24, 35}

(2) Education and training of key stakeholders, including:

- Primary care physicians, emergency physicians, and orthopedists, to improve the differential diagnosis of lower back pain.
 - Increase awareness of inflammatory back pain³¹ and “red flags” that warrant further evaluation.
 - Increase knowledge of referral criteria.³¹
 - Recommendations that do not require imaging have been published for primary care physicians for the screening and referral of patients with suspected axSpA.³⁶
 - Increase awareness of validated indices (disease activity scores and patient-reported outcomes) that can be used in daily practice.
 - Tunisian and Moroccan versions of the Bath Ankylosing Spondylitis Disease Activity Index and the Bath Ankylosing Spondylitis Functional Index have been developed.^{37,38}
 - The Assessment of SpondyloArthritis international Society Health Index has been translated into Arabic and Turkish, among other languages.³⁵
- Rheumatologists in SpA nomenclature (eg, nr-axSpA), to reduce diagnostic confusion.
- Rheumatologists and radiologists in reading and interpreting MRIs of the sacroiliac joints.³¹
 - Particular MRI sequences that are useful in diagnosing axSpA have been published.¹
- Patients and the general population through print and online educational materials, and public campaigns.
- Payers on disease burden and diagnostic and management challenges.

(3) Development of guidelines and best practices

- Rheumatologists should participate in developing local or country guidelines for disease management.
 - Cost-effectiveness studies can help inform local treatment guidelines.
- Low-cost, well-defined, locally validated diagnostic and referral tools are needed for primary care physicians.²⁰
- A low-cost, high-accuracy test using tag-single nucleotide polymorphism genotyping for HLA-B27 should be considered for routine use.³⁹
- In some countries, physicians should consider testing for HLA-B15.
 - HLA-B15 has been associated with combined peripheral and axSpA, as well as peripheral SpA, in studies from Colombia, Tunisia, Belgium, and Mexico.⁴⁰

(4) Accessibility

- Health authorities should improve patients' access to novel medications.
- Specialized SpA clinics in hospitals would be beneficial for patients and physicians.

Abbreviations: axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; nr-axSpA, nonradiographic axial spondyloarthritis.

the extent of immigration.²⁴ Also, rheumatologists in different countries may follow different treatment pathways as a result of diversity in training.

For example, in Qatar, where healthcare is provided free for nationals and at a low cost for residents, one study found that 15% of patients with axSpA were receiving a csDMARD and 40% of patients were receiving a TNF inhibitor.⁵ In Lebanon, where the healthcare system is a mix between governmental (completely free) and partial coverage, 47% of patients with axSpA and 33% with peripheral SpA had been treated with bDMARDs.²⁵ A study of patients with nr-axSpA in North Africa found Ankylosing Spondylitis Disease Activity Scores and Bath Ankylosing Spondylitis Disease Activity Index scores were suggestive of inadequate disease management.¹² Additionally, in the ASAS-COMOSPA study, only 23% of patients with SpA in Morocco and 42% in Egypt ever received a TNF inhibitor.²⁶ These findings suggest that bDMARD use is heterogeneous between countries, and these therapies are underused in some parts of North Africa and the Middle East.

7 | AUTHOR SUGGESTIONS FOR IMPROVING CURRENT PRACTICE AND FUTURE MANAGEMENT OF axSpA

Suggestions for improving the management of axSpA, based on a review of the literature as well as the experience of the authors, are provided in Table 4.

8 | SUMMARY

Early diagnosis and intervention for patients with axSpA has the potential to improve clinical outcomes as well as patients' quality of life. Therefore, it is important for clinicians to minimize the lag time between diagnosis and disease management in these patients.² In North Africa and the Middle East, this can be achieved through a clear understanding of the specific disease landscape across the region, and the use of new and existing referral and



diagnostic tools. Additionally, local or country treatment pathways should be developed that leverage the most cost-effective therapies at the appropriate stage of disease, in order to maximize the benefit for all patients.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors agree to be accountable for all aspects of the work.

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