Paper presented at East zone mid term Rheumatology CME

Patna Journal of Medicine
An official journal of *Indian Medical Association, Bihar State Branch*
www.thepjm.in

CONFERENCE PROCEEDING

Spondyloarthritis: What do we need to know?

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ABSTRACT

There has been a paradigm shift in our understanding of Spondyloarthritis in the last 3-4 decades. In the past, late diagnosis, based on radiological findings, resulted in unfavourable outcomes. Another impediment was classifying the disease traditionally into 7 sub-groups which further delayed diagnosis and treatment. Early diagnosis has become a reality with the introduction of MRI in the diagnostic armamentarium. It has also been realized that it is better to classify the disease into predominantly axial and predominantly peripheral than into 7 different sub-groups as treatment protocols depend more on clinical manifestation (axial vs. peripheral) than on nosological sub-division of the disease. The changed paradigm has resulted in better outcomes for the sufferers.

KEYWORDS: Spondyloarthritis, Armamentarium, Paradigm shift.

INTRODUCTION

Spondyloarthritis (SpA) is a group of inflammatory arthritides with common pathological and clinical features. It is the second most common arthritis in our country after rheumatoid arthritis.[1] Global prevalence ranges from 0.2 to 1.6 % across the population.[2] Disease prevalence is linked to the prevalence of the HLA B27 gene. In India, the HLA B27 gene is found in up to 6% of the population with minor variation in different parts of the country.[3] SpA primarily affects the axial skeleton (sacroiliac joints and spine). Peripheral joints are also affected and there is extra articular involvement too. Ankylosing spondylitis (AS) is the prototype of the group. Patients usually present with alternating buttock pains and chest pain being maximal in the morning (morning stiffness). There is difficulty turning in bed in the later part of the night. Peripheral joints also get involved. Extra-articular involvement affects the skin, gut, mucous membrane, eye, etc., depending upon the sub-types.

Diagnosis of SpA is challenging, more so in the early years, as clinical signs and symptoms are like those of other rheumatologic conditions. However, early diagnosis is crucial as late diagnosis results in deformities and functional impairment due to relentless inflammation. The main reason for delayed diagnosis is its dependence on radiological findings. X-ray does not pick inflammation; it picks bony changes, the sequela of inflammation. The radiological changes in AS take almost 7-10 years to be detected. In contrast, an MRI can pick up inflammation *per se*. It appears as bone marrow oedema in the scan. The introduction of MRI has revolutionized the diagnostic process of SpA. Early diagnosis is possible with this imaging modality.

The ASAS classification has brought about a conceptual change in our understanding of SpA.[4] It has subdivided SpA into two groups based on clinical manifestations of predominant axial and peripheral features rather than having 7 interrelated nosological entities traditionally. The changed concept is therapeutically relevant. This chapter will shed light on these issues.

SpA: Cardinal features

Cardinal features of SpA differentiate it from other rheumatologic conditions: -

- Seronegativity
- Male: Female 2-3:1
- Age < 45-years
- HLA B27
- Sacroiliitis, Inflammatory back pain (IBP)
- Enthesitis
- Dactylitis
- Asymmetrical oligoarthritis
- Psoriasis, IBD

SpA patients are seronegative as rheumatoid factor and anti-CCP antibodies are not detected in them, unlike RA. SpA was earlier designated as seronegative spondyloarthritis (SSA), to differentiate it from RA. Synovium is the main pathological site in RA whereas SpA primarily involves the entheses (sites of attachment of ligaments and tendons to the bone). SpA is characterized by osteoproliferation

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in place of osteodestruction seen in RA. SpA is a disease of young males. Males are 2-3 times as frequently affected as females and age at onset is usually less than 45-years. There is a striking association with the HLA B 27 gene. Inflammatory back pain (IBP) and enthesitis are the classical features of SpA. Inflammation of the sacroiliac joints is a characteristic pathologic feature of SpA. The term Spondyloarthritis is a misnomer as the main site of inflammation is the SI joint rather than the spine. The IBP due to sacroiliitis presents as alternating buttock pain which is maximal in the early morning. The pain eases as the day progresses with physical activity. It is crucial to differentiate IBP from mechanical back pain, a more common variety of back pain encountered in clinical practice. IBP improves with activity and deteriorates with rest; the opposite holds true for mechanical back pain. Another classical feature is the painful inflammation of an entire digit (Dactylitis). The digit appears uniformly swollen (Sausage digit). Apart from the primary involvement of the axial (SI joints, Spine) peripheral joints are also involved. It presents as an asymmetrical oligoarthritis with predominant involvement of the larger joints of the lower limbs. Some SpA cases are associated with Psoriasis (Psoriatic arthritis) or IBD (Enteropathic arthritis).

SpA: Classification

- Traditional classification: SpA has been classified traditionally into 7 inter-related nosological entities (Box 1)

■ Ankylosing spondylitis (AS)
■ Psoriatic arthritis (PsA)
■ Reactive arthritis (ReA)
■ Enteropathic arthritis
■ Peripheral spondyloarthritis pSpA)
■ Juvenile SpA (jspA)
■ Undifferentiated SpA (uSpA)

Box 1: Classification of Spondyloarthritis

AS is the flagship member of the group. It has predominant axial features like sacroiliitis and involvement of the spine. IBP is a characteristic clinical feature. It has been divided into a non-radiographic form (nr-axSpA) and a radiographic form, Ankylosing spondylitis. The two are believed to be a continuum, the nr-SpA being an earlier stage of the disease. The clinician is expected to pick the non-radiographic disease as radiographic changes appear after 7-10 years of the former phase. Psoriasis affects 3% of the population and 10% of them develop arthritis (PsA). It manifests as oligo or polyarthritis and dactylitis. Most patients have typical skin and nail lesions of psoriasis which aid in diagnosis. ReA follows infection elsewhere in the body, usually a gastrointestinal or a genitourinary. It presents as acute oligoarthritis predominantly affecting bigger joints of the lower limbs in a young adult, preferably a male. Enteropathic form is associated with inflammatory bowel disease (IBD) either Crohn's or ulcerative colitis. Peripheral form (pSpA) is the involvement of peripheral joints only. It is challenging to differentiate it from RA, a more common clinical entity. When SpA affects children less than 14-years of age it is jSpA. Lastly, there are undifferentiated (uSpA) case that do not fit into any of the sub-types.

- Clinical classification: Axial vs. peripheral: Assessment of Spondyloarthritis International Society (ASAS) has provided a classification of SpA more suitable for diagnostic and therapeutic purposes (Box 2).

• Predominantly axial SpA
■ Non-radiographic axial SpA (nr-axSpA)
■ Radiographic axial SpA (r-axSpA/AS)
• Predominantly peripheral SpA
■ Reactive arthritis
■ Psoriatic arthritis
■ Enteropathic with IBD
■ Undifferentiated SpA
Source: Assessment of Spondyloarthritis International Society

Box 2: Clinical Classification of Spondyloarthritis

Some of the sub-types of SpA have mainly predominant axial manifestations while others have predominant peripheral involvement. Therefore, based on the clinical presentation, SpA can be divided into two broad groups, predominantly axial and predominantly peripheral. The most common variety of SpA is the axial SpA, having predominantly axial features, i.e., involvement of SI joints and spine. Based upon the radiologic finding, it is further sub-divided into radiographic and non-radiographic forms. The less prevalent type of SpA is peripheral SpA, characterized mainly by peripheral joint involvement. This is further subdivided into ReA, PsA, IBD-related, and uSpA. It is important to note that all these forms overlap among themselves as far as their clinicopathological features are concerned. As the treatment of axial and peripheral manifestations differs (see later) the clinical classification is suitable for therapeutic purposes.

Investigation

- Acute phase Reactants: Although CRP and ESR are helpful in diagnosis, these are raised in only half of the cases.
- Imaging: Overreliance on radiological changes for diagnosis has done more harm than good to the patients of SpA. It delays the diagnosis by 7-10-years as definite changes take time to be established and picked. By the time a diagnosis is made based on clinical features and X-ray (Modified New York criteria for AS), it becomes too late as deformities set in. A Plain X-ray of the SI joint shows sclerosis, erosion, and widening of the joint space and ultimately ankylosis, an end stage of the disease. Radiological findings in the spine are squaring of the vertebrae, Romanus lesions, and the syndesmophytes culminating ultimately into typical 'Bamboo spine' found in 40% of late cases of AS.
- MRI: MRI has completely changed the diagnostic process of axSpA. Its ability to detect inflammation has become a game-changer. Short-tau inversion (STIR) sequences of SI joints showing bone marrow oedema (BMO) indicates active inflammation. The use of gadolinium or contrast is not required for routine diagnostic scans in axSpA. MRI evidence of sacroiliitis is used in the ASAS classification of axSpA (see later).
- HLA B 27: The HLA B27 gene is present in 90% of AS patients and it ranges from 50-70% for other sub-types. However, it has little diagnostic significance as it is detected in 8% of healthy subjects.

DIAGNOSIS

The guiding principle of diagnosis is to 'diagnose early.' However, diagnostic delays of several years are common, resulting in grave outcomes. In the past, Modified New York Criteria for AS classification based on X-ray as a diagnostic tool was the cause of the delay. At present, the attribution of "disc prolapse" as the cause of all the back symptoms by the lay public and sadly, by the caregivers as well, is by no means a small contributor to an erroneous and late diagnosis. We should think beyond the 'disc prolapse' too. An opportunity for effective treatment is lost due to delay in diagnosis, and inflammation goes unabated with consequent deformity.

Is early diagnosis possible?

It was made possible by introducing classification criteria for axSpA and pSpA by ASAS: -

- axSpA: The criteria can be applied to those presenting predominantly with axial features with or without peripheral involvement. The qualifying condition for entry criteria is that the patient should have back pain for 3-months or more and the age at the onset should be less than 45-years. Once the patient qualifies, he/she should fulfill the conditions of either an imaging arm or a clinical arm for diagnosis. In the imaging arm, the patient should have sacroiliitis on imaging (X-ray or MRI) plus 1 or more SpA features. The clinical arm consists of HLA B27 positivity plus 2 or more SpA features (Box 3).

Patients with back pain ≥ 3 months and age at onset < 45-years
- Imaging arm: Sacroiliitis on imagining* plus ≥ 1 SpA feature#
- Clinical arm: HLA B27 plus ≥ 2 SpA features

* Sacroiliitis on imaging: Definite radiographic sacroiliitis according to Modified New York criteria or positive MRI
# SpA features: -
- IBP
- Arthritis
- Enthesitis
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/Ulcerative colitis
- Good response to NSAIDs
- Family history of SpA
- HLA B27
- Elevated CRP

Box 3: ASAS classification criteria for axial spondyloarthritis.[5]

- pSpA: A patient having a predominant peripheral joint manifestation can be diagnosed with ASAS classification criteria for pSpA (Box 4). For qualification, the patient should have a history of arthritis, enthesitis, or dactylitis in addition to SpA features.

Arthritis or enthesitis or dactylitis (without current back pain) plus ≥ 1 of the following features
- Uveitis
- Psoriasis
- Crohn's /Colitis
- Preceding infection
- HLA B27
- Sacroiliitis on imaging

OR
- ≥ 2 of the following
- Arthritis
- Enthesitis
- Dactylitis
- IBP (Ever)
- Family history of SpA

Box 4: ASAS classification criteria for pSpA[6]

TREATMENT

One of the important rationales behind classifying SpA as predominantly axial and predominantly peripheral lies in the different treatment options available for the two. As opposed to axSpA where conventional disease-modifying agents (csDMARD) are ineffective and non-steroidal anti-inflammatory drugs (NSAID) are the only conventional treatment available, the csDMARDs are effective in the treatment of peripheral manifestations of the disease.

Exercise: Exercise is a crucial non-pharmacological intervention for axSpA. It prevents deformity and helps improve pain and stiffness. Extension exercises, cycling, and swimming are recommended.

NSAID: NSAIDs are the cornerstone of pharmacological intervention. Pain and stiffness are reduced remarkably within 48-72 hours of its introduction. It should be given as a long-acting preparation at bedtime to deal with the troublesome morning stiffness. The good efficacy of NSAID is quite interesting to note as other anti-inflammatory agents like glucocorticoid (GC) and csDMARD are much less effective in contrast to their good efficacy in RA.

GC: Surprisingly systemic GC has no role in the treatment of SpA. Intra-articular injection to an overly symptomatic joint or an area of enthesitis is the only indication in SpA. This again is quite in contrast to GC's excellent efficacy as an anti-inflammatory agent in RA.

csDMARD: It needs to be re-emphasized that csDMARDs are ineffective in axSpA, however, these agents are effective in treating peripheral manifestations of the disease. Maximal evidence is available for Sulphasalazine (SSZ); however, leflunomide and methotrexate can also be used with equal efficacy.

bDMARD: Biologics are very effective in both axSpA and pSpA. Again, in contrast to RA where a variety of biologics are effective, in SpA till recently, only TNF inhibitors were approved for use. Recently, IL 17A blocker, Secukinumab, and IL-12/23 inhibitor Ustekinumab have been approved in AS.

tsDMARD: Tofacitinib has been approved for PsA since 2012. FDA approved Tofacitinib in December 2021 in recalcitrant cases of AS but with a black-boxed warning for serious infections, mortality, malignancy, MACE, and thrombosis.

CONCLUSION

Spondyloarthritis is a constellation of inflammatory arthritides with overlapping features. Treatment outcomes have been unsatisfactory because of the delayed diagnosis and inadequate options. With a better understanding of the disease, classification criteria provided by ASAS, and an improved treatment armamentarium at disposal, better outcomes have been realized. Caregivers should embrace these changes in their day-to-day clinical practice.

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