ABSTRACT

USpA is one distinct form of spondyloarthritis in the clinical spectrum of spondyloarthritides. It is very difficult to differentiate the various forms in their early stages due to their overlapping clinical features. These are asymmetric lower limb arthritis, enthesopathy, unilateral or bilateral sacroiliitis, rheumatoid factor negativity, extra articular features like uveitis, familial aggregation and association with HLA B27.

USpA differs in some ways like late age of onset, female preponderance, insidious course, less of acute flares, low incidence of uveitis and HLA B27 positivity. Dactilitis (Sausage digit) is also a characteristic feature. There is no involvement of spine and very rarely unilateral sacroiliitis.

Some isolated syndromes like syndrome of Seronegativity, Enthesopathy and Arthropathy (SEA) in children, ankylosing tarsitis involving tarsal region with plantar fasciitis, acute iritis, aortic incompetence and heart block are variants of USpA.

In various cohort analysis it was found that about 30-40% proceed to develop AS in about 10 years and some 50-60% remain USpA, 10-15% go into spontaneous remission and about 1-2% manifest as psoriatic arthritis.

Prognostically they are better than other forms of SpAs. Most patients maintain good function without progressive disease or clinically significant radiographic changes. Treatment with NSAIDs is effective. Salazopyrin has been found to be effective in a large multicentre trial. Use of TNFα blockers have been advocated in severe forms of USpA.

ABBREVIATION USED


INTRODUCTION

Spondyloarthropathies constitute a spectrum of inter related and overlapping family of related disorders that include ankylosing spondylitis (AS- the prototypical spondyloarthropathy), reactive arthritis (ReA, previously known as Reiter syndrome, RS), psoriatic arthritis (PsA), arthritis associated with crohn’s disease and ulcerative colitis, juvenile Ankylosing Spondylitis (JAS), undifferentiated spondyloarthropathy (USpA) and possibly behcet disease and whipple disease (1,2).

It is very difficult to differentiate these various types in their early stages due to their overlapping clinical features. The common denominator of all these is the pathological sites of inflammation which include the entheses, which are the sites of bony insertion of ligaments and tendon, the sacroiliac joints and the axial skeleton, large joints of lower extremity in asymmetric fashion and some extra-articular structures like eyes, skin, gut, aortic valve and conducting tissues of heart (3,4).

The association between seronegative oligo or polyarthritis and spondyloarthritides was first described by Moll and weight is mid seventies (5).

The characteristic features of SpA are:

1. Asymmetric peripheral arthritis predominantly of lower limbs.
2. Radiographic sacroiliitis with or without spondylitis
3. Enthesopathy.
4. Absence of rheumatoid factor
5. Absence of subcutaneous nodules and other extra articular features of RA
6. Anterior uveitis
7. Increased familial incidence
8. Association with psoriasis, IBD, urogenital infections
9. Presence of dactylitis
10. Strong association with HLA B27
ETIOPATHOGENESIS & HLA-B27 LINKAGE

The precise etiology of spondyloarthopathies is unknown but involves the interaction of genetic and environmental factors. There are strong association with some subtypes of HLA B27 which supports the view that the disease is due to genetically determined immune response to environmental factors in susceptible individuals (6, 7). Out of over 25 subtypes of HLA B27, HLA B2705, 2702, 2704 & 2707 are clearly associated with risk of Spa (8). Two subtypes, HLA B2706 (southeast Asia) and 2709 (sardinia) are not associated with Spa (8, 9). Association of Spa with HLA B27 positivity is further vindicated by the fact that the incidence of Spa in Eskimo and Inuit persons is highest with HLA B27 positivity of 25-40% (10) and rare in Japanese persons with a very low (<1%) prevalence of HLA B27 (11). HLA B2705 is the major sub-type present in 90% of HLA B27 positive whites and 45% of HLA B27 positive Asian Indians (7).

Association of various spondyloarthopathies with HLA B27 is given in table 1.

Indian Scenario - HLA B27 in south India is positive in 83% of AS patients (12) and 94% of AS patients in North India (13).

HLA- A locus has been associated with uveitis in North India (14) and HALA2 has been found in high frequency in and around Pune (15).

PATHOPHYSIOLOGY

The primary pathology of any type of SpA is enthesitis. This is mediated normally by CD4 and CD8 T lymphocytes and macrophages leading to elaboration of cytokines particularly tumor necrosis factor α (TNF-α) and transforming growth factor β (TGF-β). This enthesopathy occurs at sites which bears greater physical stress viz spinal ligaments, calcaneum & planter fascia. Other pathological sites of inflammatory changes are sacroiliac joints, axial skeleton, limb joints and some nonarticular structures like the gut, skin, eyes and aortic valves (16).

CLINICAL PRESENTATION

As the spondyloarthopathies have some common clinical features, I will first discuss the prototypical ankylosing spondylitis and then proceed to elaborate the characteristic features of undifferentiated SPA.

1. Inflammatory back pain – most common first manifestation – detailed below.

2. Peripheral enthesitis – Achilles tendons, calcaneus, metastarsal heads, tibial tuberosity, iliac crest, greater trochanter, ischial tuberosity, costochondral junction.

3. Asymmetric peripheral arthritis of lower limbs particularly hips and knees.

4. Dactylitis – Sausage digits – usual in reactive arthritis, psoriatic arthritis and undifferentiated Spa.

5. Extra-articular features:
   a. Anterior uveitis AS - 20-30%
      ReA - 5-10%
      USpa - 2-5%
      PsA - <1%
   b. Cardiovascular – (10%) – Aortitis, AR, AV Block
   c. Pulmonary – restrictive lung disease, bilateral apical fibrosis (AS)
   d. G.I – Asymptomatic inflammation of terminal ileum and proximal colon seen in 60% cases of AS & USpa.
   e. Neurological – Cauda equina syndrome, compressive myelopathy.
   f. Renal – amyloidosis, NSAID nephropathy, IgA nephropathy.
   g. Metabolic bone disease – Osteopenia & osteoporosis in long standing cases.

INFLAMMATORY BACK PAIN

Most common symptom and the first manifestation in about 75% of patients (17).

New criteria has been proposed (18)

1. Morning stiffness lasting more than 30 minutes
2. Improvement of back pain with exercise but not rest
3. Diffuse non-specific radiation of pain into buttocks (alternating buttock pain)
4. Nocturnal back pain during second half of night only

When 2 of the 4 are present – sensitivity is 70.3% and specificity – 81.2%

DIAGNOSTIC CRITERIA OF SPONDOYLOARTHOPATHY.

There are two sets of criteria which are sensitive and specific.

ESSG – (European SpA study group) criteria (19)

1. Inflammatory spinal pain or synovitis – asymmetrical or predominantly in the lower limbs >3 months
2. And one or more of the following

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**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>American white – 92%</td>
</tr>
<tr>
<td></td>
<td>African Americans – 50%</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>60-80%</td>
</tr>
<tr>
<td>Psoriatic SpA</td>
<td>60%</td>
</tr>
<tr>
<td>IBD associated SpA</td>
<td>60%</td>
</tr>
<tr>
<td>Isolated acute anterior uveitis</td>
<td>50%</td>
</tr>
<tr>
<td>Undifferentiated SpA</td>
<td>20-25%</td>
</tr>
<tr>
<td>Healthy white American</td>
<td>8%</td>
</tr>
</tbody>
</table>
a. Alternate buttock pain
b. Sacroiliitis
c. Enthesitis
d. Inflammatory bowel disease
e. Positive family history of SpA
f. Psoriasis
g. Urethritis or cervicitis or acute diarrhea within one month

Amor Criteria (20)
- Inflammatory back pain 1
- Unilateral buttock pain 1
- Alternating buttock pain 2
- Enthesitis 2
- Peripheral arthritis 2
- Dactylitis (Sausage digit) 2
- Acute anterior uveitis 2
- HLA B27 positive or family history of SpA 2
- Good response to NSAIDs 2

A SCORE OF 6 OR MORE IS DIAGNOSTIC OF SpA

Apart from these two general criteria of SpA, there are two criteria for the diagnosis of Ankylosing Spondylitis

New York criteria (1984)
- Inflammatory low back pain
- Limitations of lumbar spine motion in sagittal and frontal planes
- Decreased chest expansion (>3cm)
- Bilateral sacroiliitis grade 2 or higher
- Unilateral sacroiliitis grade 3 or higher

Definite A.S. when 4th or 5th criterion present with any clinical criteria.

Rome criteria (1961)
- Inflammatory back pain and stiffness for >3months
- Pain and stiffness in the thoracic region.
- Limited motion in the lumbar spine
- Limited chest expansion
- History of uveitis

Diagnosis of AS – when clinical criteria with bilateral sacroiliitis grade 2 or higher

Undifferentiated spondyloarthropathy – How does it differ from other SpAs.

Undifferentiated spondyloarthropathy is a syndrome with features similar to other spondyloarthropathies, but affected patients do not fulfill criteria for any specific spondyloarthropathy. According to various cohort studies, they may represent either an incomplete form of ankylosing spondylitis or other forms of reactive arthritis or IBD associated spondyloarthropathy.

However, more recent studies suggest that they represent a distinct disease entity based on demographic and clinical criteria.

The differentiating features of SpA include –

1. it is more common in female – with a male : female ratio – 1:3 (AS- 3:1)
2. It is generally found in late young to middle aged adults with a peak onset at around age 50 years.
3. It is not associated strongly with HLA B27 according to Western data it is more prevalent in whites than in non white ethnic groups (21).
4. It carries good to excellent prognosis. Erosive arthritis is very uncommon, fusion of spine and advanced sacroiliitis is rare.
5. Dactylitis is more common

Clinical features of undifferentiated SPA (1,21)

1. Age of onset: young to middle aged with a peak onset at around 50 years

Table 2: Diagnostic Criteria

Although no specific criteria are identified, modified Amor Criteria can be helpful in confirming a clinical diagnosis (21)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory back pain</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral buttock pain</td>
<td>1</td>
</tr>
<tr>
<td>Alternate buttock pain</td>
<td>2</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>2</td>
</tr>
<tr>
<td>Asymmetric peripheral arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Dactylitis (sausage digit)</td>
<td>2</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>2</td>
</tr>
<tr>
<td>HLA B27 positive or family history of SpA</td>
<td>2</td>
</tr>
<tr>
<td>Good response to NSAIDs</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Diagnosis of USpA with 6 or more points

Exclusion criteria
- Diagnosis of specific spondyloarthropathy
- Sacroiliitis on radiograph ≥grade 2
- Precipitating genitourinary or GI infection
- Psoriasis
- Keratoderma blenorrhagicum
- IBD (Crohn disease or ulcerative colitis)
- Positive antinuclear antibody titre> 1:80
Undifferentiated Spondyloarthropathy: Diagnostic Challenge & Therapeutic Options

2. The male to female ratio – 1:3
3. Onset – usually insidious
4. Clinical features is given in table 4
5. Even after years of active disease, sacroillitis and spondylitis are either absent or very mild.
6. Extra articular manifestations are uncommon occurring in less than 10% of patients – they are anterior uveitis, oral ulcers, rash, nonspecific IBD, Pleuritis and pericarditis.
7. Prognosis – Although most patients have chronic, active disease and require long term therapy, some patients have mild and intermittent symptoms requiring only intermittent symptomatic therapy.

Period of active disease may last from 1-2 weeks to several months interspersed with long asymptomatic period.

OTHER CLINICAL VARIANTS OF USpA
1. A syndrome of seronegativity, enthesopathy and arthropathy (SEA) has been described in children which is clinically similar to undifferentiated SPA. These children often develop ankylosing spondylitis over time with typical radiographic changes, usually in early adulthood. (22,23).
2. Ankylosing tarsitis – seen in children presenting with enthesitis in the tarsal region. There may be subsequent ossification (23).
3. Syndrome of acute anterior uveitis (acute iritis), aortic incompetence and heart block with no signs of arthritis or may accompany or precede the onset of spondyloarthropathy – (24,25)

In one scandinavian study, more than 80% of male patients without arthritis and with aortic regurgitation and severe cardiac conduction disturbance were positive for HLA B27. (26)

DIAGNOSTIC WORK UP

Laboratory investigation – none are specific.

- Rheumatoid factor and ANA- -ve
- ESR & CRP is elevated in 75% of patients and may correlate with disease activity.
- Creatine kinase (CK) is occasionally elevated but not associated with muscle weakness.
- Serum IgA level may be elevated, correlating with elevated acute phase reactants
- HLA B27 – 92% of AS patients compared to 25% of USpA are HLAB27+Ve

Routine HLA B27 testing is not necessary. However it is helpful only in certain circumstances like syndrome of acute anterior uveitis and in patients suspected having a SpA especially in populations with a low prevalence of HLA B27 like Japanese persons.

IMAGING

1. Standard radiography -
   - In AS sacroiliitis is usually bilateral, symmetric and gradually progressive over years.
   - In AS – spondylitis starts in the lumber or thoracolumbar spine and progresses proximally in a continuous fashion.
   - In ReA & PsA – sacroiliitis is asymmetric and spondylitis is discontinuous
   - In USpA – sacroiliitis and spondylitis is very rare but there are erosions, periosteal new bone formation and finally ossification at insertions of Achilles tendon and the plantar fascia and the calcaneum.

Grades of sacroiliitis on plain x-ray – 0-normal, 1- possible, 2-minimal, 3-moderate, 4-completely fused.

2. MRI & CT – may show early evidence of sacroiliitis, erosions and enthesitis not apparent on plain x-ray.
MRI using fat saturating techniques like – short tan inversion recovery (STIR) or MRI with gadolinium are sensitive for inflammatory lesions of enthesitis.

NATURAL COURSE OF UNDIFFERENTIATED SpA

Evidence based study of USpA outcome. Two important studies will be discussed here briefly.

The natural course of USpA is variable.

In some patients symptoms disappear after a single or a few episodes of activity while in others the disease progresses to A.S. or other defined spondyloarthropathies after recurrent episodes or persistent inflammation of the entheses and synovial joints.

In a study by Mau et al on 54 patient of USpA, 59% patients fulfilled the criteria for AS at the 10 year follow up (27).

In another study by sampaio Barros et al, 68 patients of USpA fulfilling ESSG criteria of SpA were followed up for 2 years. After 2 years, following outcomes were observed: USpA- 75%; disease remission-13% AS- 10%, psoriatic arthritis-2%. Buttock pain and

Table 4: Clinical features of undifferentiated SPA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory back pain</td>
<td>90%</td>
</tr>
<tr>
<td>Buttock pain</td>
<td>80%</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>75%</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>40%</td>
</tr>
<tr>
<td>Dactylitis (sausage digits)</td>
<td>20%</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>1-2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55%</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>32%</td>
</tr>
<tr>
<td>HLA B27 +ve</td>
<td>25%</td>
</tr>
</tbody>
</table>
positive HLA B27 were statistically associated with progressions to a definite SpA (28).

In a recent report of Mexican spondyloarthropathy group – 62 patients of USpA were followed up for a mean period of 3.3 years (range-3-5years). 42% patients fulfilled the criteria for AS after 3.3years, an incidence rate of 0.13 cases per year. They also observed that patients who became AS had more flares of disease activity throughout the follow up resembling previous reports of high ESR or c- reactive protein associated with A-S. (30)

TREATMENT STRATEGIES

1. NSAIDs – they are the starting point of treatment. Non-selective like indomethacine & Naproxan and selective COX-2 inhibitors Etoricoxibs are equally effective but should be given in full therapeutic doses.

2. DMARDs – Efficacy of sulphasalazine in the treatment of peripheral arthritis has been shown in 10 controlled studies, including 2 large multicenter studies in the US and France (85,86).

   In a recently published multicentre randomised controlled European trial – 230 patients of active USpA or AS with symptom duration less than 5 years were randomly assigned to 24 weeks treatment with SSZ 2gm/day or placebo. The authors observed that patients with inflammatory back pain (IBP) and no peripheral arthritis had significantly (p=0.03) more benefit with SSZ. Spinal pain (p=0.03) and morning stiffness (p=0.05) improved with SSZ in these patients compared to placebo. This study was the first study to be carried out on the use of DMARDs in patients with USpA and early AS with IBP being the leading clinical symptom.

   The efficacy of SSZ for axial symptoms in USpA is very interesting according to this study (31).

3. TNFα Blockers : Infliximab & Etnercept are available in India.

   Currently their used is recommended in established AS and psoriatic SpA.

   However the grey areas are those USpAs who may well progress to full AS with its concomitant functional and structural morbidity.

   Two open level studies on treatment with TNFα blockers in patients with severe, active USpA have shown marked benefit on spinal pain, peripheral arthritis, BASDAI, BASFI and quality of life – with Etanercept (32) and Infliximab (33).

   However it is not rational as far as pharmacoeconomics is concerned to treat these patients with TNFα blockers. Moreover it is not recommended in USpA and for that matter even in early AS ignoring a therapeutic window for SSZ.

OTHERTHERAPIES

Methotrexate has been used with success in early AS and USpA with peripheral arthritis.

Bisphosphonates have modest effect on disease activity is both AS & other forms of SPA including USpA.

CORTICOSTERIODS

Local corticosteroid injections are helpful in symptomatic enthesis, plantar fasciitis and secroiliitis.

CONCLUSION

Undifferentiated SPA may represent an early phase or incomplete form of ankyloisng spondylitis or another form of spondyloarthropathy. Recent data from various cohort studies however suggest that these patients may represent a distinct disease entity based on demographic and clinical criteria like, later age of onset, female preponderance, insidious onset, low HLA B27 positivity, rarer extra-articular manifestation and good prognosis without progressive disease or clinically significant radiographic changes. More than 50% cases dever prngress to AS or any other form of spondyloarthopathy.

Most of the patients respond wellto NSAIDs. Use o& SSZ, methotrexate and even TNFα blockers can be used in a minority of cases.

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