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SPONDYLOARTHRITIS (MA KHAN, SECTION EDITOR)

Seronegative Arthritis in South Asia: An Up-to-date Review

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Abstract This article summarises the available information on seronegative arthritides from South Asian countries, namely India, Pakistan, Bangladesh, Sri Lanka, Nepal, and Bhutan. The diseases described are spondyloarthritides (SpA), including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease-related arthritis (IBDa), enthesitis-related arthritis (ERA) of the paediatric age group, and undifferentiated spondyloarthritis (uSpA). Relevant information on SpA from South Asia is scarce. However, the available publications indicate that these are commonly seen conditions. HLA-B27 is present in approximately 6–8 % of the normal population in the Indian subcontinent. In the SpA group, HLA-B27 has the highest frequency in AS patients (>90 %) and the lowest in PsA patients. Clinical features are similar to those reported in standard textbooks, but with a few exceptions: e.g., in South Asian countries ERA is the most common subset of juvenile idiopathic arthritis (JIA), whereas in the West the most common subset of JIA is oligoarthritis. Poverty is a major challenge in treating these diseases in South Asia; with poor health insurance coverage, only a few patients are able to afford biological treatment. Therefore, rheumatologists have attempted novel treatment strategies for those with an unsatisfactory response to standard non-steroidal anti-inflammatory drugs (NSAIDs) or coxibs.

Keywords Seronegative arthritis · Seronegative spondyloarthritis · Ankylosing spondylitis · Undifferentiated spondyloarthritis · Psoriatic arthritis · Psoriatic spondyloarthritis · Reactive arthritis · Reiter's disease · Inflammatory bowel disease-related arthritis · Enthesitis-related arthritis · Juvenile idiopathic arthritis · India · Pakistan · Sri Lanka · Bangladesh · Nepal

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Introduction

In present-day terminology, the term "seronegative arthritis" is used almost exclusively for spondyloarthritis (SpA). The concept of SpA evolved in the 1970s in the United Kingdom to describe a closely associated group of conditions with specific common clinical, epidemiological, genetic, and radiographic characteristics [1, 2], including AS, PsA, IBDa, and ReA. In the paediatric age group the terminology used to describe SpA was confusing. The current ILAR system of JIA has most children with SpA classified as ERA; a few may be also classified as PsA or as undifferentiated [3••]. It is possible that a unifying classification for this group of children could be

provided by the Assessment of SpondyloArthropathy International Society (ASAS) criteria of axial and peripheral manifestations [4, 5••], which have been recently revealed by our group to be 100 % sensitive [6•]. Patients who cannot be classified in any of the defined categories are described as having undifferentiated SpA (uSpA).

In this paper, reports of SpA from South Asian countries, including India, Pakistan, Bangladesh, Sri Lanka, Nepal, and Bhutan, are discussed. It is to be noted that publications on this topic from South Asia are scarce, and most are rather old. Therefore, this review has some inbuilt limitations.

Epidemiology

SpA and/or AS

There are only a few epidemiological reports on SpA and/or AS from South Asia.

India

There are two reports on the prevalence of AS from India, both from its Western region (Maharashtra), describing an AS prevalence of approximately seven and of nine per 10,000 population [7, 8]. A large hospital-based study from southern India reported 0.6 % of patients to have AS; 87 % were HLA-B27 positive [9]. Some hospital-based studies from India have reported uSpA to be the commonest subset [10, 11]. Such patients could be suffering from forme-fruste of Reiter's disease, induced by a wide array of gut and genitourinary infections [12]. These studies were performed before the publication of the ASAS classification criteria for axial and peripheral SpA [4, 5••]. Therefore, these conclusions may not reflect the actual status in the community.

Pakistan

The prevalence of SpA/AS among Pakistanis from Karachi (southern part of Pakistan) and those living in United Kingdom has been reported to be approximately 0.95 per 1000 population [13]. Another paper from northern Pakistan (different ethnic group, mostly of Punjabi) reported the prevalence of SpA of only 0.1/1000 population, which is much less than that reported by workers from Karachi [14].

Bangladesh

The prevalence of SpA and/or AS in Bangladesh has been reported to be approximately four per 10,000 [15].

No reports could be found on the prevalence of SpA and/or AS in other countries in South Asia.

Psoriatic Arthritis

India

Psoriatic arthritis is a common form of arthritis seen in rheumatology clinics in South Asia. In a prospective study on 18,924 patients seen at a dermatology department in Delhi, 530 (2.8 %) were diagnosed with psoriasis, of whom 290 (55 %) had joint symptoms, 40 (9 %) were diagnosed with arthralgia, seven (1.3 %) with deforming variety of arthritis, and one (0.2 %) with bilateral sacroiliitis [16]. In another study from southern India, on 141 patients with PsA, classified according to Classification Criteria for Psoriatic Arthritis (CASPAR) [17], spondyloarthritis was present in 29 (20.6 %) [18•]. This is in contrast with earlier reports of 11.2 % and 12.1 % of patients presenting with spondyloarthritis [19–21]. However, it is to be noted that, whereas the older papers used Moll and Wright criteria for psoriatic arthritis [1], the paper by Mithun et al. used CASPAR criteria [18•].

No reports could be found on the prevalence of PsA in other countries in South Asia.

Juvenile Spondlyoarthritides (jSpA) or Enthesitis-related Arthritis (ERA)

There is a large gap in the literature on jSpA or ERA from South Asia. No data on this topic have been published from Sri Lanka, Pakistan, Nepal, or Bhutan. There are a few publications from India on the etiopathogenesis, the clinical features, and the articular damage related to this disease [22, 23•], but none on epidemiology.There is only one report from Bangladesh of tarsitis in a child with ERA [24].

Despite the lack of epidemiological studies on JIA from South Asia, most paediatric rheumatologists have noted, and some papers have also confirmed, that within the broad category of JIA, ERA is the most common JIA among Indian patients. This is in contrast with the West, where oligoarthritis is the most common JIA [25••]. In India, both at the community level in the State of Maharashtra (West India), as reported by Kunjir et al., and in a hospital setting in Delhi, ERA is the most common category, including 36–40 % of all JIA patients [26, 27]. There are older reports from India that classified patients with juvenile arthritis by the American Rheumatism Association (ARA) criteria, which did not distinguish SpA subtypes. In the previous systems most ERA patients were classified as "pauciarticular type II", which was reported to have a prevalence of 30–47 % [28, 29].

Genetic Studies

HLA-B27 in Normal Population

India

HLA-B27 is a highly diverse gene that occurs with a frequency of ~90–95 % in Asian-Indian patients with SpA, compared with its frequency of 6 % in healthy controls [30–32]. In northern India (around Delhi), the predominant subtype was B*27:05, observed with a frequency of 58 %, followed by: B*27:04, with a frequency of 31 %, predominantly occurring in oriental populations; B*27:07, with a frequency of 9 %, observed mostly in Asians; and B*27:02, with a frequency of 1 % [33, 34]. Studies performed in the population around Mumbai revealed the presence of the same four alleles (B*27:02, 27:04, 27:05, 27:07) and of some uncommon alleles, including 27:08, 27:14 [35], and B*27:18 [36]. In another population, from the Kerala state of South India, only two subtypes, B*27:05 and B*27:04, were observed [37]. Other subtypes, including B*27:01, 27:06, 27:09–13, 27:15–17, and 27:19–107, have not been reported among Indians.

Pakistan

HLA-B27 positivity amongst normal healthy kidney donors from Karachi in southern Pakistan was reported to be 5.5 % [38]. Professor M.A. Khan has quoted an HLA-B27 prevalence of 6–8 % in Pakistan [39].

No other reports on the prevalence of HLA-B27 in South Asian normal population were found.

Genetic Studies of the SpA Group of Diseases

India and Pakistan

The first paper describing the frequency of HLA-B27 among AS patients from India was a report from Chandigarh (northern India) in 1977 [30]. Among 17 AS patients and 60 controls, the frequency of HLA-B27 was reported to be 94 % and 3 %, respectively. The first description of the association of HLA-B27 with AS patients, among Punjabis from Pakistan, was a brief report published in 1977 [40]. There were 45 patients with AS; HLA-B27 was screened in five of them, and all were positive. In 1979 our group reported on HLA-B27 among patients in the broad SpA category, and found 90 % to be HLA-B27 positive [31]. In 1984 our group studied HLA-B27 in 51 AS patients and 118 normal controls [32]. Ninety-four per cent of patients, as compared with 6 % of controls, were HLA-B27 positive. In an earlier paper, our group from Delhi reported on HLA-B27 in 29 patients with different subsets of SpA, and in 118 normal controls [41]. HLA-B27 was positive in 84 % of patients, but only 5.9 % of controls.

Disease Associations with HLA-B27 Subtypes

Studies performed in India have reported a strong association of AS and/or SpA with HLA-B27 subtypes [30–32]. As mentioned above, in 1983 our group reported HLA-B27-positivity in 84 % of uSpA patients, and a higher relative risk of other antigens including A11, Aw30, A28, Bw63, Bw41, B37, and Bw35 [40]. Initial studies by our group also revealed an association of B*27:05 and B*27:04 with AS, whereas B*27:07 was observed in Northern-Indian AS patients with a frequency similar to that observed in healthy controls [33, 34]. In contrast, B*27:02 was rare and observed only in patients with acute anterior uveitis [33, 34]. These observations were confirmed for a larger disease cohort, suggesting an association of B*27:05 with SpA, and of B*27:04 with, primarily, AS [42]. Studies conducted in Mumbai (western India) reported an association of B*27:05, B*2704, B*27:14, B*27:07, and B*27:02 with AS, whereas B*27:08 was observed more frequently among haemophilia patients with chronic synovitis [43••, 44]. Among Southern-Indian AS patients, the predominant association observed was with B*27:05 and B*27:04; no other subtypes were observed in this cohort [37]. Another study, on AS patients living in the Mumbai region of western India, has confirmed a strong association of B*27:05 with AS, and a similar association for other subtypes including B*27:04, B*27:07, and B*27:02 [36]. Thus, in summary, the B27 subtypes most associated with AS in Asian Indians are B*27:05, B*27:02, B*27:04, and B*27:07.

These findings may be compared with the association of HLA-B27 with AS and/or SpA in other populations. The most commonly observed associations are with B*27:05, B*27:02, B*27:04, and B*27:07. Several other subtypes, including B*27:01, B*27:02, B*27:03, B*27:04, B*27:05, B*27:07, B*27:08, B*27:10, B*27:13, B*27:14, B*27:15, B*27:19, B*27:23, B*27:24, B*27:25, and B*27:49, have also been reported to occur among patients, even if one case only [45, 46••].

There are no studies reporting on HLA-B27 subtype distribution in AS and/or SpA patients from Sri Lanka, Bangladesh, Nepal, and Pakistan.

MHC loci other than HLA-B27 in AS and/or SpA

Our studies revealed that MHC loci other than the HLA-B27 also determine susceptibility to spondylitis. For example, whereas HLA-A2 and HLA-B27 were both elevated in patients with AS and unclassifiable arthritis, patients with Reiter's disease had a lower frequency of B35 and B27 [47]. Another study evaluating MHC haplotypes, including MIC and TNF polymorphisms, in AS patients (Indians,

Caucasians, and Africans) revealed that B27 alone, rather than B27-related class I haplotypes, contributes to AS susceptibility. Further interesting observations were seen when the MICA (MHC class I-like A) gene was evaluated with the B27 gene, as MIC-B27 haplotypes, for example: MICA-A4 with B*2705,02,03 and 08; MICA-A5 with B*2704 and B*2707; and MICA-A.5.1 with B*2706 [48]. Among SpA patients from southern India, significant association has been reported with an extended six-locus haplotype B*2705-Cw*02-STR-MICA (A4)-C1_4_1 (213 bp)-C1_2_5 (178 bp)-MIB (340 bp) [37]. In this study, a significant positive association of HLA-B27 and Cw*02 with SpA was also reported, whereas B*44 had a negative association. Studies on B7 CREG alleles in patients from the Mumbai region reported significantly increased frequencies of HLA-B7 and HLA-B40 alleles in HLA-B27− patients compared with the HLA-B27+ group [49].

AS and/or SpA-associated Uveitis

In Asian-Indian patients with AS and/or SpA-associated uveitis, the most frequent HLA phenotype observed was A9-B27, whereas A2-B27 has been observed to have the highest frequency among both white and black American patients [50]. A more recent study on AS and SpA-related uveitis in Asian Indians reported more AS patients carrying B*27:04 than carrying B*27:05, and that B*27:02 was rare and observed only in patients with acute anterior uveitis [33, 34]. Another paper reported on 89 patients with endogenous uveitis (80 with acute anterior uveitis), of whom 56.3 % were HLA-B27 positive [51•]. This figure was much lower than the 64.3 % reported earlier from Chandigarh (northern India) [52].

Nepal

In a recent paper from Nepal, the frequency of HLA-B27 among patients with SpA, classified according to ASAS criteria, was reported to be 52.9 % [53•], which is among the lowest reported from this region of the world. The prevalence of HLA-B27 in the normal Nepalese population is not known.

HLA-B27 prevalence in AS and/or SpA has not been reported from other South-Asian Countries.

Genetic Studies in PsA

The prevalence of HLA-B27 in psoriatic arthropathy has been reported to be 11.3 % in Indians [18•]. This is lower than the 19–30 % reported from other regions of the world [54–57]. On the basis of the available evidence, the authors concluded that HLA-B27 is associated with spondyloarthropathy [55–60]. However, the prevalence was much lower than that associated with AS (prevalence of the antigen was more than 90 %) [61]. Studies from other countries have reported an association between palmo-plantar pustulosis and HLA-B27 positivity [56, 62]. However, Mithun et al. found no such association [19]. Extra-articular features were less prevalent [19]. As well as HLA-B27, which has a significantly higher prevalence in PsA, association of PsA with HLA-B38, B8, and C6 was observed by Canadian workers [54].

Genetic Studies on Unclassifiable (Undifferentiated) SpA (uSpA)

One of the earliest studies from India reported HLA-B27 in 84 % of uSpA patients. The relative risk of some other antigens, including A11, Aw30, A28, Bw63, Bw41, B37, and Bw35, was also higher [41].

Disease Associations with HLA-B27 Subtypes

Prevalence of HLA-B27 in psoriatic arthropathy has been reported to be 11.3 % in Indians, as against 30 % in Caucasians [18•]. As well as HLA-B27, which has a significantly higher prevalence in PsA, association of PsA with HLA-B38, B8, and C6 has been observed in other populations [54].

In a paper on juvenile SpA from Varanasi (northern India), urinary tract infection, diarrhoea, and constipation were more common in HLA-B27+ cases [63]. In a report from Mumbai, HLA-B27 alleles were characterized in a sample population of 51 persons [64]. B*2704, B*2705, B*2707, B*2708, and B*2714 alleles were detected, and two novel B27 alleles, B*2708 and B*2714, were found in this Indian population. In addition, B*2714 was observed in a patient with AS. This association was not previously reported in ethnic groups from India. In another study, workers from northern India looked for additional genetic factors in AS, because the contribution of HLA-B27 to disease susceptibility is only 15 % [65]. They studied IL-1-receptor-antagonist polymorphism in Indian patients with AS. This large study concluded that the IL-1RN*2 allele is a susceptibility marker for AS in the Indian population, but that it does not affect disease phenotype.

There are no studies reporting HLA-B27 subtype distribution and disease association among populations from Sri Lanka, Bangladesh, Nepal, and Pakistan.

Studies on Pathogenesis

Microbial Antigens in Joint Fluid in Reactive Arthritis and Undifferentiated Arthritis

In a South Indian cohort, significantly elevated IgG response against culture supernatant proteins of three organisms—lipopolysaccharides of *Escherichia coli*, *Klebsiella*, and *Salmonella typhi*—was noted in AS and ReA patients [66]. In a study from Mumbai, the workers used PCR to look for antigens of some of the microbes previously implicated in ReA [67]. Salmonella-genus-specific DNA was detected in

synovial fluid (SF) of three acute post-dysenteric ReA patients, but not in any other samples or in control samples. *Chlamydia trachomatis* and *Mycobacterial tuberculosis* (MTB) antigens were not detected in any sample. MTB DNA was detected in most samples. The authors concluded that salmonella may have a function in the pathogenesis of ReA. In a study from northern India, investigators sought to identify immunogenic peptides from HLA-B*27:05-binding salmonella outer-membrane proteins (OMP) in patients with ReA and/or uSpA [68•]. Using highly sophisticated techniques, they were able to identify nine novel immunogenic OMP peptides binding to HLA-B*27:05 that had sequence similarities with other arthritogenic bacteria.

There have been several publications from India on the etiopathogenesis of the ERA and jSpA group. Although the exact pathogenesis is unknown, enteric bacteria implicated in reactive arthritis could be responsible for exacerbation of disease in ERA. Corroborating evidence is available: antigen-specific lymphoproliferative responses were observed in 14 of 26 patients with ERA [69]. The same group of workers also revealed innate immune-gene dysregulation involved in antigen presentation, scavenger function, chemotaxis, and proteases [70•]. Workers postulated that continuing disease, even in the absence of infection, indicates a probable function of endogenous ligands in the activation of Toll-like receptors (TLRs) and the persistence of disease. A calcium-binding protein complex of myeloid-related proteins (MRPs) 8 (S100A8) and 14 (S100A9), expressed by granulocytes, monocytes, and macrophages on activation, is an endogenous ligand for TLR4. This has been studied by Rahman et al., and revealed to be increased in the plasma of ERA patients and higher in those with active disease [71•]. However, no specific polymorphisms in TLR2 and TLR4 have been found in ERA patients [72]. Upregulation of TLRs and their adaptors (probably in response to microbial inducers) has been revealed, which probably leads to uncontrolled inflammation and tissue injury. [73•]. In another study, the same group revealed that stimulation of TLRs with their ligands leads to increased production of proinflammatory cytokines and matrix metalloproteinases (MMPs) by fibroblast-like synoviocytes derived from the synovial fluid of children with ERA [74]. Finally, a study from the same centre revealed that in patients with ERA, peripheral blood Th1, Th2, Th17, and T_{reg} cells were unchanged, but Th1 and Th17 cells were increased and Th2 cells were reduced in SF compared with blood [75].

Clinical Characteristics of Ankylosing Spondylitis, Spondyloarthritis, and uSpA

India, Bangladesh, Nepal

The earliest report from South Asia was on 25 patients (22 males and three females) from our group, with seronegative peripheral arthritis, affecting primarily the large joints of the lower limbs, and with other typical features of SpA, e.g. heel pain, lower-back pain, and mucosal ulcers [41]. However, their disorders could not be categorised under any subset of spondyloarthritis: neither AS, Reiter's disease, inflammatory bowel disease (IBD)-associated SpA, nor any other. The mean age of onset was 21.4 years, 60 % of patients had mono or oligoarthritis, and 60 % had arthritis of only lower-limb joints. Knee, ankle, and hip joints were most commonly involved, often asymmetrically (mean degree of asymmetry=0.28). Minimal radiographic sacroiliitis was present in only four patients, although 13 had lower-back pain. HLA-B27 antigen was detected in 21 (84 %) of these patients, and only 5.9 % of 118 controls (relative risk 83). An additional four patients had isolated severe bilateral heel pain: three of them were positive for HLA-B27. We believe that in present-day terminology (using appropriate classification criteria, e.g. Amor [76], ESSG [77], or ASAS [5••, 6•]) this group of patients would be classified as suffering from "undifferentiated SpA". Soon after the publication of this paper, Borges et al. analysed arthritis of $\geq$6 weeks duration among 86 young males and 122 young females followed over three years [78]. The study included patients between 16–40 years of age. Of the 86 males, 52.3 % had SpA, whereas only 9.8 % of the 122 females had SpA. HLA-B27 was not reported.

In an early paper (1984) from South Asia, using the Rome classification criteria [79], we reported 41 patients with AS from Delhi [32]. Since then there have been additional reports on AS and/or SpA from different centres in India [79–83], all using the modified New York classification criteria [85], and from neighbouring countries [53•, 86] using ASAS criteria [5••, 6•]. Table 1 summarises the results of these studies, including that from Bangladesh and Nepal.

There are several interesting features among these studies. Probably the most intriguing observation is with regard to the male-to-female ratio. Earlier studies reported a ratio markedly skewed in favour of males (16:1). There are many possible reasons for the skewed male-to-female ratio in older studies (Table 1) [80, 87]. Since those earlier years, much more information has become available, clearly indicating that females may have more subtle and less severe symptoms that could have led to under-diagnosis.

Sri Lanka

There is one case report from Sri Lanka of an AS patient with "bamboo spine", syndesmophytes, and sacroiliitis [88]. His oligoarthritis was aggravated after a diarrhoeal episode. The additional clinical features included keratoderma blenorrhagica and circinate balanitis. HLA-B27 was positive. Erythrocyte sedimentation rate (ESR) was 115 mm h^{-1}, and reactive protein was 96 mg dL^{-1}. Rheumatoid factor (RF) was also positive, at 64 IU mL^{-1}. The authors mentioned that the

Table 1 Ankylosing spondylitis vs. SpA: comparison of clinical characteristics and HLA-B27 prevalence in different studies from India and South Asia

Characteristics of AS	Delhi (Northern India) 1984 n=51 [32] (Rome criteria) [79]	Mumbai (Western India) 1989 n=82 [80] (mNY criteria) [85]	Chennai (Southern India) 1990 n=102 [81] (mNY criteria) [85]	[5] Bangladesh 2007; n=61 (45 adults, 16 juveniles) [86] (ESSG criteria) [77]	[3] Delhi 2009 n=70 [83, 84] (mNY criteria) [85]	[6] Nepal 2012, n=102 M=66, F=36 [53•] (ASAS criteria) [5••, 6•]
Age of onset (yrs)	21.2	M 20.56; F 25.4	26	M 24±2.6; F 28±2.2 M 24±2.6; F 28±2.2	M 23.6; F 32.5	39.1±14.9 (15–75)
Disease duration	–	–	–	M 5.5 (0.25–20); F 6.5 (0.25–20) units needed	–	30 months
Delay in diagnosis (yrs)	–	M 6.3; F 5.71	–	–	–	–
Male-to-female ratio	16:1	7.2:1	16:1	5.8:1	5:1	1.8:1
Symptoms at onset (%)						
Peripheral arthritis (number of cases)	47 (knee 11 (21.5 %), hip 15 (29.9 %)), ankle, shoulder and elbow 1 each (1.96 % each)	38 (46.3 %) M 49.97 %; F 20 %	38/102	–	–	–
Inflammatory back pain and/or neck pain	51 %	42 (51.2 %): M 34 (47.2 %), F 8 (80 %); cervical spine pain 2 (2.4 %)	59/102	–	–	–
Peripheral + axial involvement	–	–	–	20 (33.3 %)	–	–
Acute anterior uveitis	10 %	1 (1.2 %)	11/102	Conjunctivitis 3 (4.8 %)	25.7	2 (1.96 %)
Enthesitis	2 % (heel pain)	NA	18/102 (heel pain)	41 (68.6 %)	–	56 (54.9 %)
Clinical features (%) *Authors need to decide whether to give all figures in %. If yes, they should change table entries to reflect this decision. If not, they should remove the unit from this box.*						
Inflammatory spinal-sacroiliac symptoms (back pain)	100	82 (100 %)	–	26 (41.4 %)	–	45 (44.1 %)
Peripheral arthritis: mainly knee, ankle, hip, oligo, prominent asymmetry	61 %	Overall 39 %	48 %	26.6 %	65.7	Small joints 29 (28.4 %); large joints 72 (70.6 %)
Enthesitis	Heel pain 24	NA	Heel pain 35/102; costo-sternal 11/102	Overall 41 (68.6 %)	Achilles tendonitis 24.3 %; costo-sternal 30 %	NA
Anterior uveitis/iridocyclitis	11 (22 %)	M 0, F 1 (1.12 %)	14/102	–	87.1	NA
Urethritis/mucositis	8 (18 %)	NA	NA	–	NA	NA
Reiter's type features	–	–	–	4 (6.6 %)	–	NA
Renal disease	5 (10 %)	NA	–	–	0	–
Apical pulmonary fibrosis	2 (4 %)	NA	5/102	–	NA	–
Aortic incompetence	2 (4 %)	NA	8/102	–	NA	–

Table 1 (continued)

Characteristics of AS	Delhi (Northern India) 1984 $n=51$ [32] (Rome criteria) [79]	Mumbai (Western India) 1989 $n=82$ [80] (mNY criteria) [85]	Chennai (Southern India) 1990 $n=102$ [81] (mNY criteria) [85]	[5] Bangladesh 2007; $n=61$ (45 adults, 16 juveniles) [86] (ESSG criteria) [77]	[3] Delhi 2009 $n=70$ [83, 84] (mNY criteria) [85]	[6] Nepal 2012, $n=102$ M=66, F=36 [53•] (ASAS criteria) [5••, 6•]
HLA-B27	48 (94 %)	M 46/59 (78 %), F 8/9 (88.88 %)	–	–	92.9 %	54 %
Family history	–	Overall 34 %; M 23 (32 %), F 5 (50 %)	–	4 (6.6 %)	–	–
Radiographic sacroiliitis	51 (100 % by selection criteria)	100 % (by definition)	80/102	16 (24.4 %)	87.1 %	33 (32.3 %; MRI available only for 4 that showed sacroiliitis) (no mention of if only 33 patients had sacroiliitis on standard radiography, or if it was performed only for those 33 patients
ESR (mm h^{-1})	–	–	–	–	51.45±28.9	–
CRP	NA	NA	NA	NA	NA	NA

mNY criteria = modified New York classification criteria; ESSG criteria = The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy; ASAS criteria = Assessment of SpondyloArthritis International Society classification criteria

presence of a significant titre of RF could not have been incidental. The question of whether there was an overlap between these two diseases was raised.

The overall clinical pattern of AS and/or SpA described from this region is fairly uniform, and similar to that reported from other parts of the world (Table 1). Inflammatory axial involvement and sacroiliitis were common. Enthesitis was present in high numbers of patients. The male-to-female ratio and the delay in presentation were similar to those described in several older reports from around the world (Table 1).

Clinical Characteristics of Psoriatic Arthritis

Table 2 gives the demography, clinical characteristics, and HLA-B27 status of PsA patients from South Asia [19, 21, 89–91].

The first publication on PsA from India was by our group in 1984 [21]. The paper described 20 patients with PsA, their clinical features, and their HLA-B27 status. Since then, several studies from India and other countries in South Asia have been published. The results are summarised in Table 2.

Clinical Features of jSpA in South Asia

Detailed clinical presentation of jSpA has been described by our group in 2006 [22] and 2012 [6•]. Patients were usually boys, with predominant lower-limb oligo disease and enthesitis. Isolated inflammatory back pain was uncommon, but did occur with peripheral joint disease in some children. Tarsitis was a common feature. Of the 124 children with ERA, 102 (82 %) were boys. Median age of onset was 10.9 years; median delay to diagnosis was 5 months. Of this set of children 64 (51.6 %) had arthritis and enthesitis. Sixty (48.3 %) had enthesitis or arthritis and two or more of the following: sacroiliac (SI) tenderness and/or inflammatory spinal pain was present in 28 % (22.6 %), HLA-B27 was present in 97.6 %, a family history of medically confirmed HLA-B27-associated disease was reported for 9.7 %, anterior uveitis was present in 16.1 %, and onset of arthritis in boys older than six years of age in 83.8 %.

Of note, 72 % of children in this category did not have inflammatory back pain [6•]. Kunjir et al. obtained similar findings in a community study near Pune (Western India), in which they reported the clinical features of all JIA patients [26]. In their cohort of 235 JIA patients, 84 (35.7 %) had ERA. Of those with ERA, the median age of onset was 13 years, 10 % were females, 19 % had SI joint disease, and 37 % had enthesitis. 88.7 % were HLA-B27 positive: lower than the percentage reported at our centre in Delhi (see above).

In a retrospective study on 210 patients with AS, Aggarwal et al. reported that 30 % had their disease onset at <16 years of age, and that these patients had a higher incidence of

Table 2 Demography, clinical characteristics, and HLA-B27 status in psoriatic arthritis

Demography and clinical characteristics	Delhi (1984) *n*=20 [21]	Mumbai (1995) *n*=102 [89]	Chennai (2003) *n*=116 [19]	Pakistan (2008) *n*=37 [90]	Pakistan (2009) *n*=46 [91]
Male-to-female ratio	1.85:1	1.83:1	2:1	2.85:1	2.44:1
Age of onset of psoriasis (yrs)	NA	Males 33, females 28	NA	4.5 years before the onset of arthritis (range 0.5–20)	NA
Mean age of onset of arthritis (yrs)	16–60 (mean not available; male and female age distinction not available)	38 for both males and females	41 (range 10–65)	44 (range 23–60)	39.8 (range 5–75, most common from 31 to 45)
Median interval between the onset of psoriasis and arthritis (yrs)	NA	2.5	2.8	4.5	NA
Psoriasis onset (antedated arthritis in (%))	12 (60 %) (Psoriasis persisting at onset of joint disease in 9 (45 %))	64 (63.8 %)	58 (50.8 %)	44 (100 %)	NA
Psoriasis and arthritis simultaneously	NA	20 (19.7 %)	43 (37.1 %)	NA	NA
Psoriasis subsequent to the onset of arthritis	40 %	5.8 %	12.1 %	NA	NA
Psoriasis not observed	NA	12 (11.6 %)	–	–	0 %
Polyarticular arthritis	6 (30 %; 1 was seropositive RA overlap)	26 (25.4 %)	48.3 %	43.2 %	NA
Mono-oligo-spondyloarthritic, enthesopathic arthritis	5 (25 %); HLA-B27 positive in 3 (60 %)	51 (50 %; HLA status not reported)	48.3 %	35.2 %	62.9 %
Mutilans variety	1 (5 %; HLA-B27 positive)	1 (0.98 %; HLA status not reported)	0.86 %	2.7 %	0 %
DIP-only	2 (40 %)	1 (0.98 %)	2.6 %	18.9 %	6.5 %
Joints affected	Limited details available	Limited details available	–	Detailed break-down NA	–
Spine-sacroiliac	5 (25 %)	26 (25.5 %)	–	5 (13.5 %)	41.3 %
Knee	NA	Among the most common	66.4 %	NA	76.1 %
Ankle	NA	Among the most common	50 %	NA	28.37 %
Hip	NA	NA	5.2 %	NA	NA
Foot	NA	NA	Toes 33.6 %, MTP 19.8 %	NA	NA
Shoulder	NA	NA	25.9 %	NA	34.8 %
Elbow	NA	NA	30.2 %	NA	34.83 %
Joints in the hand-fingers	NA	Among the most common	MCP 52.6 %, PIP 34.5 %	NA	30.4 %,
Wrist	NA	–	35.3 %	NA	NA
DIP only	2 (10 %)	1 (0.98 %)	32.8 %	7 (18.9 %)	30.4 %
Mutilans variety	3 (15 %)	2 (1.96 %)	0.86 %	1 (2.7 %)	–
Sausage digits	NA	30 (29. 4 %)	16 %	NA	NA

NA = not available; PIP = proximal interphalangeal joint; DIP = distal interphalangeal joint; MTP = metatarsophalangeal joint

peripheral joint disease and valvular disease when compared with patients who had their disease onset in adulthood [92].

These studies confirm that peripheral joint disease is a common feature in children with ERA. These features have not been described in detail by any other paediatric rheumatology group from South Asia. There is only one study from Bangladesh that reports the association of tarsitis with inflammatory back pain [24].This association has been seen in 33 %

of a cohort of 110 ERA patients, as reported by us in 2012 [22].

Reiter's Disease

In 1983 my group published findings on 36 patients with Reiter's disease [93]. The male-to-female ratio was 4:1. The mean duration at presentation for males and females was 5.5 and 6.5 years, respectively. The mean age of onset was 24 and 28 years for males and females, respectively. In 75 % of patients the onset was in the second or third decade of life. Clinical manifestations included: inflammatory back pain in 69 %; mono or oligoarthritis, mainly affecting large joints in lower extremities with significant asymmetry, in 83 %; non-specific urethritis in 53 %; heel enthesitis in 44 %; radiographic sacroiliitis in 42 %; conjunctivitis in 39 %; dysentery in 33 %; mucosal ulcerations in 17 %; renal disease in 14 %; anterior uveitis in 19 %; and keratoderma blenorrhagicum in 8 %.

AS and/or SpA—comparison of South Asians with other Ethnic Groups

Uppal et al. compared clinical features of persons of South Asian (SA) ethnicity with those of Middle-Eastern Arabs (MEA) residing in Kuwait [82]. There were 26 SA and 29 MEA patients. These workers concluded that most SA patients present with uSpA, whereas MEA patients presented with AS. Family history was less common in SA patients, and peripheral arthritis was more common in SA patients.

A recent study compared phenotypic and clinical differences between Caucasian and South Asian patients with PsA living in North-East London [94]. The study enrolled 151 Caucasians and 66 South Asians diagnosed as having PsA using CASPAR criteria. The paper concludes that South-Asian patients may develop PsA earlier in life than Caucasian patients do, but their clinical characteristics are generally similar.

Complications of SpA

Amyloidosis

In a paper published in 2007 from a northern Indian city, 7 % of AS patients with disease duration longer than five years were found to have subclinical amyloidosis by abdominal subcutaneous fat-pad aspiration [95].

Renal Involvement in the SpA Group of Conditions

Our group studied renal involvement among 50 patients with SpA who carried HLA-B27 genes [96]. The study included 23 patients with AS, 16 with Reiter's disease, 10 with unclassifiable SpA, and one patient with features of SpA overlapping with rheumatoid arthritis. Nine of these patients (4.5 %) had significant persistent proteinuria. Renal biopsy in seven of them revealed proliferative glomerulonephritis. Immunofluorescence studies revealed immune-complex deposition in only three of them, but circulating immune complexes were present in five of seven patients with proteinuria. However, serum complement levels (C3 and C4) were normal in these patients, and antinuclear antibody was negative by immunofluorescence.

Laboratory Features of SpA

Radiography in AS

In a 1984 paper on AS from our group, radiographic sacroiliitis grade II or III was reported in all patients (by definition) [32]. It was bilaterally symmetrical in all except one patient. Twenty-seven (53 %) of these patients had grade II and 24 (47 %) had grade III radiographic changes, and the severity of these changes correlated well with the duration of disease. Although radiographs of the lumbar spine were not available for all the patients, clinically completely rigid spine and kyphosis were seen more frequently in patients with longstanding disease.

In more recent paper on AS from our group, radiographic bilateral sacroiliitis involvement was reported in 87.1 % (61/70), grade II in 57.1 % (40/70), grade III in 15.7 % (11/70), and grade IV in 14.2 % (10/70) [83]. Radiographic spine involvement was seen in the lumbar region 77.0 % (54/70), thoracic region 53.1 % (34/64), and cervical region 42.2 % (27/64), with the whole spine involved in 39.0 % of patients (25/64).

A report from Pakistan describes MRI findings in the spines of three patients with AS [97]. The reported findings included florid anterior spondylitis (Romanus lesion), florid discitis (Andersson lesion), ankylosis, insufficiency fractures of the ankylosed spine, syndesmophytes, arthritis of the apophyseal and costovertebral joints, and enthesitis of the interspinal ligaments.

Radiography in Psoriatic Spondyloarthritis

In 2003, Rajendran et al. from Chennai (southern India) described radiographic findings for 116 patients with PsA [19]. Thirteen (11.2 %) had bilateral involvement. In the lumbar spine, non-marginal syndesmophytes were noted in six patients (5.2 %) and squaring of the vertebrae in one patient (0.86 %). Of the six patients with joint erosions (5.2 %), five had erosions in the proximal and/or distal interphalangeal joints of their hands, and one in the metatarsophalangeal joint of the foot. In four patients, tendoachilles calcification (3.5 %) was observed. One patient

(0.86 %) had "pencil-in-cup" deformity. The mean time taken for the peripheral joint erosions to occur in their patients was 34.2 months.

Acute Phase Reactants in AS and/or SpA

Most of the studies from South Asia quoted in this paper did not report on acute phase reactants. The exception is a 2009 report by our group [83]. In this study, 51.45 % patients were reported to have high ESR. No C-reactive protein (CRP) report was available.

Acute Phase Reactants in PsA

A study on PsA from Mumbai (western India) reported: ESR >20 in 60/85 patients (70.5 %) and >100 in 9/85 (10.5 %); haemoglobin (Hb) <10 in 10/96 (10.4 %); serum uric acid >6.5 in 6/42 (14.2 %); and RF in 6/41 (14.6 %) [89]. Radiography was not reported. Roussou et al. reported on PsA in three ethnic groups living in North-East London [94]. They found elevated ESR (average 20.5±17.6) in 23.9 % of Asian females, which was not significantly different from other races.

In their series of 116 patients with PsA, Rajendran et al. [19] reported elevated ESR and C-reactive protein in 51.7 % and 43.9 % of patients, respectively. RF was positive in 3.4 %, and antinuclear antibody (ANA) was present in 5.4 % (3/56) of patients. Anaemia (Hb<10 g dL^{-1}) was observed in four patients (3.4 %).

Immunological Studies

In 1983 our group published findings regarding some basic immunological variables among patients with SpA [98]. There were 29 patients with AS, 15 with Reiter's disease (RD), and 10 with uSpA, with 27 controls. All tests were not performed in each patient. IgG levels were significantly elevated in 19/19 AS patients, 15/15 patients with RD, and 9/9 with uSpA. Serum IgA was significantly elevated in RD patients, but not in the other two groups. One patient with "unclassified" seronegative spondyloarthritis had complete absence of IgA and IgM in his serum [99]. Serum C3 levels were estimated in 26 AS patients, 14 RD patients, and nine unclassified seronegative spondyloarthritis patients. There was no significant difference from 27 controls. Autoantibodies were not detected in any of the 29 patients with AS, 15 with RD, and 10 with uSpA. Circulating immune complexes were detected, by latex agglutination-inhibition, in 5.9 % of 85 controls, 61 % of 18 patients with AS, 67 % of 15 patients with RD, and 78 % of nine patients with uSpA. On the basis of these findings, the authors suggested a possible on-going antigenic challenge, with immune stimulation and tissue damage.

Treatment of AS and/or SpA in South Asia

There are no controlled trial reports from South Asia. There are two open trials, summarised below.

The main challenge in this part of the world is the extreme poverty and poor health insurance coverage. There could be many reasons for this, the discussion of which is beyond the scope of this article. However, it is of practical relevance. Biologicals being among the most expensive drugs, their use in South Asia is almost out of the question. For this reason, rheumatologists try out novel therapy for patients who fail to achieve satisfactory disease control with standard anti-inflammatory drugs (non-steroidal anti-inflammatory drugs (NSAIDs) or coxibs). Thus, we treated 46 patients with sulfasalazine, methotrexate, and intermittent "intravenous pulses" of synchronised pamidronate and methylprednisolone [100]. Of these, 39 patients achieved ASAS-20 and BASDAI-50 response (85 %, 95 % CI, range 71 % to 94 %); 7 (15 %) patients failed to improve. The expense of six months of treatment was approximately 10-fold less than that of anti-TNF alpha treatment over the same period of time.

Another, more recent attempt to reduce the cost of treating SpA has been reported from southern India [101•]. Twenty-four patients were given a short course of infliximab at 0, 2, 6, and 14 weeks, while continuing on sulfasalazine (SSZ) and methotrexate (MTX). The mean duration of follow-up was 9.1 months. Statistically significant reductions in tender and swollen joint count, BASDAI, and BASFI as compared with baseline were noted at all three visits; the fall in ESR and CRP was statistically significant at one and three months, but not at last follow-up. It was concluded that continuing SSZ and MTX after a short course of infliximab results in sustained improvement for patients with SpA.

Conclusions

The SpA group of conditions is common in rheumatology clinics in South Asian countries, but authentic data on epidemiology are scarce. In contrast, extensive information is available on genetics of SpA, especially the status of HLA-B27 in the general population and in patients with the SpA group of diseases. Unfortunately, published information on clinical aspects of SpA is old; most dates from before the publication of ASAS classification criteria, making it difficult to properly categorise such patients. Because of poverty and poor health insurance coverage, use of biologicals is extremely low.

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Compliance with Ethics Guidelines

Conflict of Interest Anand N. Malaviya has served on boards for and received honoraria from Johnson & Johnson, Bristol-Myers Squibb, Pfizer, Roche, Sanofi Aventis, IPCA, and Reddy's, and has had travel/accommodations expenses covered/reimbursed by Johnson & Johnson, IPCA, and Sanofi Aventis. Sujata Sawhney, Narinder K. Mehra, and Uma Kanga declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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