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HLA B27 related 'unclassifiable' seronegative spondyloarthropathies

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SUMMARY Twenty-five patients (22 males and 3 females) are described who had 'unclassifiable' seronegative peripheral arthritis affecting mainly the large joints of the lower limbs with other typical features of spondyloarthropathies such as heel pain, low back pain, and mucosal ulcers. But their disorders could not be diagnosed as any specific spondyloarthropathy such as ankylosing spondylitis, Reiter's disease, etc. The mean age of onset of disease was 21·4 years and 60% of them had mono- or oligoarthritis; 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 4 patients, though 13 had low back pain. HLA B27 antigen was detected in 21 (84%) of these patients and only 5·9% of 118 controls (relative risk 83). In addition to these 25 patients there were 4 others whose only symptom was severe bilateral heel pain: 3 of them were positive for HLA B27.

Seronegative polyarthritis is a heterogeneous clinical entity frequently seen in rheumatological practice. The condition in most of the patients may ultimately evolve into seropositive erosive rheumatoid arthritis or into one of the group of diseases collectively identified as seronegative spondyloarthropathies, usually associated with the genetic marker HLA B27.[1-4] Over the past 5 years this laboratory has been studying the latter group of rheumatic syndromes as seen in the north Indian population.[5,6] It was repeatedly observed that some patients did not fit into any of the well defined rheumatic categories of this broad group—namely, classical ankylosing spondylitis, Reiter's disease, psoriatic spondylarthropathy, arthritis of inflammatory bowel disease, and Behçet's syndrome. Yet their clinical presentation has been so uniform that the diagnosis is easy—but of course without name. To the best of our knowledge this entity remains unnamed.

Here we report our experience with 29 patients with this clinical entity seen during a prospective study of 2 years. In the absence of any recognised name for the disease these patients were identified as 'unclassifiable' seronegative spondylarthropathy.

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Materials and methods

Consecutive unrelated Indian patients attending the immunology clinic of the All-India Institute of Medical Sciences Hospital were selected for study. All of them were seen by 2 of the authors (A.N.M. and S.P.) and questioned in detail about their joint symptoms, heel pain, low back pain or stiffness, mucosal and skin lesions, symptoms of acute anterior uveitis, conjunctivitis, urethritis, inflammatory bowel disease, and venereal exposure. Their past and family histories of these disorders were also recorded, and wherever possible the affected relatives were examined. A thorough physical examination was done, with special attention to the joints, spine, skin, eyes, buccal mucosa, and genitalia.

Tests for rheumatoid factor in sera by a standard latex agglutination test with the Rheuma-Welcotest kit (Burroughs-Wellcome, UK), postero-anterior (prone) and oblique (15°) *x*-rays of the sacroiliac joints, and tissue typing for HLA A and B loci antigens employing the NIH 2-stage microlymphocytotoxicity test[7] were done on all the patients. The clinical diagnosis was made independently of the result of the histocompatibility test. The controls for histocompatibility testing were 118 unrelated healthy volunteers.

The patients who could be given the diagnosis of the following diseases were excluded: (1) Ankylosing

spondylitis according to the Rome criteria[8]; (2) Reiter's disease—seronegative peripheral arthritis with nonspecific urethritis or dysentery or conjunctivitis or anterior uveitis; (3) psoriatic arthritis as diagnosed or suspected by the presence or past history of characteristic skin lesions or nail pits or involvement of distal interphalangeal joints; (4) inflammatory bowel disease; (5) Behçet's syndrome as diagnosed by the triad of recurrent oral and genital ulcerations and recurrent iritis.

After the exclusion of patients with the above diseases, most of those included under the group 'unclassifiable' seronegative spondyloarthropathy had seronegative peripheral arthritis and/or heel pain with the following clinical features (1) low back pain and/or stiffness with or without minimal sacroiliitis; (2) buccal or genital ulcerations; (3) family history of any of the specific spondyloarthropathies; (4) peripheral arthritis which was to some extent assymmetrical, often oligoarticular, and mainly affecting the lower limbs. The degree of asymmetry of peripheral arthritis was calculated as the proportion of joints involved asymmetrically.[9]

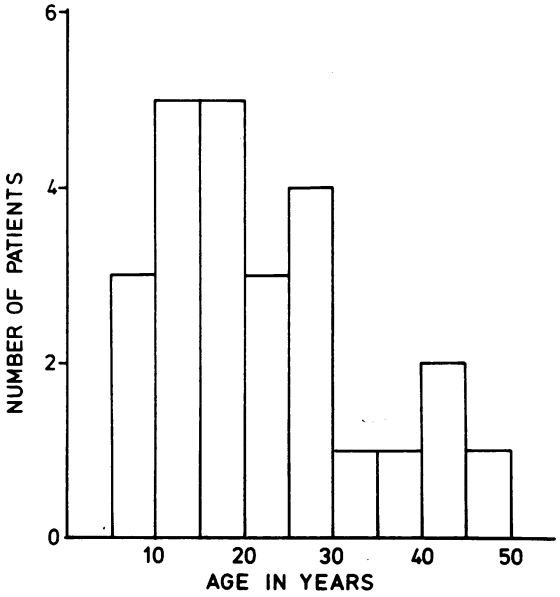

Fig. 1 *Age at onset of 'unclassifiable' seronegative peripheral arthritis in 25 patients.*

Results

A total of 133 patients with seronegative spondyloarthropathies were seen: ankylosing spondylitis 51; Reiter's disease 36; 'unclassifiable' seronegative spondyloarthropathy (SSA) 29; 'inflammatory' low back pain without *x*-ray changes of sacroiliitis 11; ulcerative colitis with arthritis 3; and Behçet's disease 3. Depending on the major presenting manifestations the patients with 'unclassifiable' SSA were divided into 2 groups: (*a*) seronegative peripheral arthritis; and (*b*) enthesopathy (Achilles tendonitis).

(A) 'UNCLASSIFIABLE' SERONEGATIVE SPONDYLOARTHROPATHY—PERIPHERAL ARTHRITIS

This group included 25 patients—22 males and 3 females. The mean age of onset of disease was 21·4 years and in 68% of them the disease started in the second and third decades (Fig. 1).

The onset of disease was insidious in 13 (52%), subacute in 10 (40%), and acute in 2 (4%) cases. The first manifestation was peripheral arthritis in 23 patients, bilateral heel pain in one, and low back pain in one. The average duration of symptoms was 4·7 years (range 3 weeks to 24 years); it was less than 1 year in 7 (28%), 1 to 5 years in 11 (44%), 6–10 years in 5 (20%), and more than 10 years in 2 (8%) patients.

Peripheral arthritis was the major manifestation in these 25 patients. Twenty-three (92%) had peripheral arthritis at the onset of disease. The average number of joints affected in the 23 patients was 3·2 (range 1–22). The number of joints involved was 1 in 5 patients, 2 in 14, 4 in 1, and more than 4 in 3 patients. Weight bearing joints of the lower limbs were affected commonly (Fig. 2, Table 1). The mean degree of asymmetry of peripheral arthritis at the onset of disease was 0·48.

During the course of the disease all the 25 patients had peripheral arthritis. The average number of joints affected was 6·8 (range 1–26). The number of joints involved was 1 in 2 (8%) patients, 2 in 6 (24%), 3 in 5 (20%), 4 in 2 (8%), 5–10 in 5 (20%), and more than 10 in 5 (20%) patients (Fig. 3). The disease affected mainly the lower limb joints (Fig. 2, Table 1). Often the arthritis was asymmetrical (the mean degree of asymmetry was 0·28).

Seven of the 25 patients had heel pain over the insertion of the tendo Achillis or os calcaneum, and 3

Table 1 *Distribution of peripheral arthritis in patients with 'unclassifiable' seronegative spondyloarthropathy (peripheral arthritis)*

	At onset (n = 23)		*During the course of disease (n = 25)*	
	Number	*Percent*	*Number*	*Percent*
Only upper limbs	3	13·0	0	0
Only lower limbs	19	82·6	15	60·0
Both upper and lower limbs	1	4·4	10	40·0

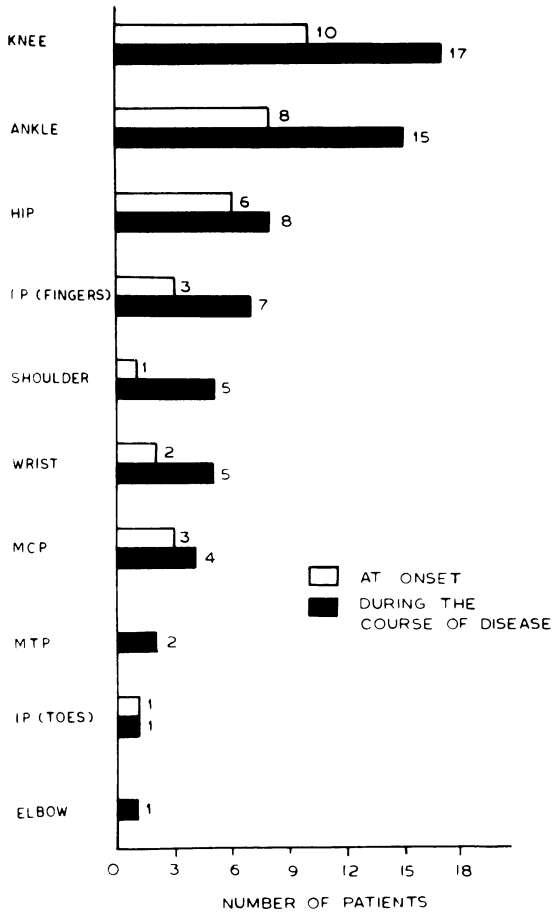

Fig. 2 *Pattern of peripheral joint involvement at the onset (23 patients) and during the course (25 patients) of 'unclassifiable' seronegative peripheral arthritis. IP = interphalangeal. MCP = metacarpophalangeal. MTP = metatarsophalangeal.*

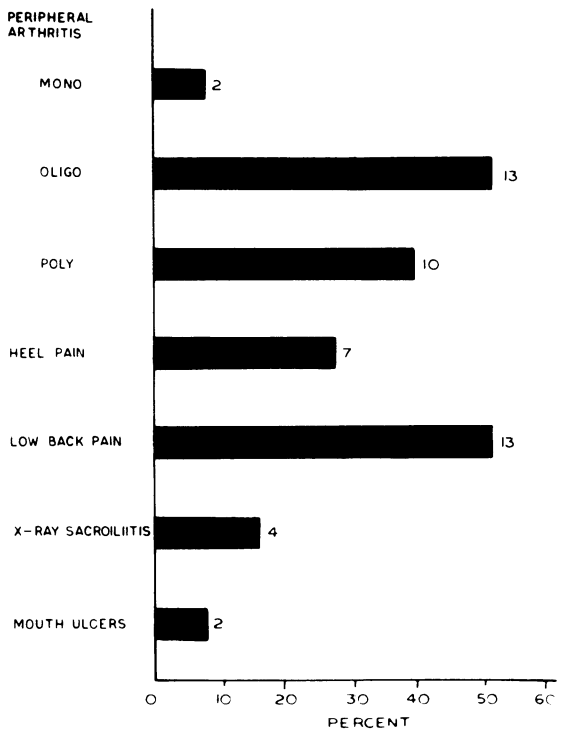

Fig. 3 *Clinical manifestations in 25 patients with 'unclassifiable' seronegative peripheral arthritis.*

had sole pain (Fig. 3). Though more than half the patients (13) had low back pain or stiffness, only 4 of them had radiographic changes of minimal sacroiliitis—that is, loss of clear-cut corticated joint space with subchondral erosions. Three patients had bilateral and one had unilateral sacroiliitis on *x*-ray. Except for the recurrent oral ulcers in 2 patients no other extra-articular features were seen in the 25 patients (Fig. 3).

Three patients had a family history of spondyloarthropathy: one patient's brother had ankylosing spondylitis, another's aunt (father's sister) had Reiter's disease, and one patient's daughter had ulcerative colitis with arthritis.

Histocompatibility testing results revealed the presence of HLA B27 antigen in 21 (84%) of 25 patients and 5·9% of 118 controls with a relative risk of 83·2 (corrected Fisher's test, $p = 6{\cdot}55\ E-14$). None of the other HLA A or B loci antigens deviated significantly from the expected frequency in these patients, though the relative risks were slightly high for some of the other antigens: A11, 3·4; AW30, 2·7; A28, 2·6; BW63, 5·3; BW41, 2·6; B37, 1·7; and BW35, 1·3. The number of HLA B27 negative patients is so small that their comparison with HLA B27 positive patients is not justified.

Twenty-four of the 25 patients were seronegative for rheumatoid factor but one seropositive (titre 1:160) patient was also included in this group because of the presence of pain over the insertion of the tendo Achillis and bilateral grade I radiographic sacroiliitis. He was 40 years old and had had arthritis for 2 months. His first symptoms were pain and swelling of both ankle joints and bilateral heel pain. Within 2 months he developed pain and swelling of the knees, wrists, and small joints (metacarpophalangeal and proximal interphalangeal) of both

hands. He also had pain in both hips, shoulders, and low back pain with marked morning stiffness of joints. He was positive for HLA B27 antigen.

(B) 'UNCLASSIFIABLE' SERONEGATIVE SPONDYLOARTHROPATHY-ENTHESOPATHY

In addition to the 25 patients described above there were 4 other patients who presented with bilateral heel pain. Three of them were men. None of the 4 patients had peripheral arthritis, low back pain, or *x*-ray changes of sacroiliitis. Except for the episcleritis in the female patient no other extra-articular feature was present in these 4 patients. They were also seronegative for rheumatoid factor, and all the 3 male patients carried HLA B27 antigen. Two of them had HLA B40 also.

Discussion

The present study describes a clinical entity of oligo- or polyarthritis seen predominantly in young males. The main features include prominent involvement of the lower limbs with asymmetry; a proportion with enthesopathy, mild radiographic sacroiliitis and low back pain, and painless mucosal ulcerations; some have a family history of one of the well defined entities within the broad group of spondyloarthropathies. All of them were seronegative, and HLA B27 was present in a large proportion of them. Yet they could not be classified into any of the well defined clinical entities.

Recently 2 other series have appeared describing a similar entity.[10 11] The peripheral arthritis described in these studies is identicial to that of the present series. However, the present series is more homogeneous, as more importance was attached to the associated features considered typical of HLA B27 related peripheral arthritis, namely, enthesopathy, low back pain and stiffness, mucosal ulcerations, and a positive family history.[1 3] This could be the reason for the higher male to female ratio and larger percentage with HLA B27 as compared with the other two series.[10 11]

The possibility that the condition of the patients in the present series will ultimately evolve into ankylosing spondylitis, Reiter's disease, psoriatic arthritis, or any of the other well defined diseases of the group must be seriously considered. Many of these patients have had the symptoms for several years, a feature against the possibility of this entity being the precursor of any of the well defined syndromes. Yet it may be years before frank skin lesions of psoriasis develop or changes of classical ankylosing spondylitis appear.[1 3]

Similarly, the clinical entity of so called 'incomplete' Reiter's syndrome is virtually identical to the present series in the mean age of onset, male sex preponderance, pattern of peripheral arthritis and the HLA B27 positivity.[12] But in the absence of urethritis and/or conjunctivitis it would be difficult to conceive the disease as Reiter's disease in any form.

Recently Keat *et al.*[13] have suggested a broad definition for the so called 'reactive' arthritis, including the sexually acquired, enterocolitic, and the idiopathic forms. Thus it is possible that the high prevalence of diarrhoeal and enteric diseases in India is responsible for the disease of at least some of the unclassified patients. Mild or asymptomatic enteric infections must be taken into account. Meanwhile this entity needs wider recognition and a suitable name.

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