

Similarity between chronic reactive arthritis and ankylosing spondylitis. A 32-35-year follow-up study

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Abstract

Objective. We assessed the long-term outcome of recent reactive arthritis (ReA) during 1973-2007 and ankylosing spondylitis (AS) during 1973-1997 to identify similarities in manifestations of disease.

Methods. Radiographs of the sacroiliac, hand and foot joints were taken at onset and at 8, 20, and in ReA 32 years from entry among recent-onset (<6 months) patients; 60 with ReA and 17 with AS. Sacroiliacal joints using the modified New York 1984 criteria and the Larsen score of 0-100 of 20 joints of hands and feet were assessed. The number of swollen joints, patients with orthopaedic operations or iritis or HLA-B27 or retirement because of spondyloarthritis, and ESR were recorded.

Results. The onset age of 60 ReA patients (34 men) was 17-54 years, mean 32 (SD 10) and 51 (85%) were HLA-B27 positive. The number of onset swollen joints was 1-5, mean 2.6 (SD 1.6), while in 40 patients at the 30-year check-up it was 0-3, mean 0.2 (SD 0.6). ESR was at onset mean 55 mm/h (SD 33) and at the 30-year check-up 15 mm/h (SD 11). *Yersinia enterocolitica* type 3 antibodies were raised in 22 (37%) patients at onset. The end-point Larsen score was 2-6, mean 4 in 6 patients. One ankle joint arthroplasty and five smaller operations had been performed. Bilateral grade 2-3 sacroiliitis developed in 9/60 (15%), and unilateral grade 2-4 in 3. The incidence of iritis was 12/60 (20%). Erosive arthritis or iritis or sacroiliitis developed in 24/60 (40%) participants. Thirteen (22%) retired because of arthritis while five died. Of 17 AS patients (8 men), whose age was initially 21-50 years, mean 33 (SD 10), 11 (65%) had rheumatic symptoms years before our first examination. All were HLA-B27 positive and developed grade 2-4 bilateral sacroiliitis during the 20-year follow-up. The end-point Larsen score was 2-22, mean 9 (SD 8) in 5 patients. Hip arthroplasties were performed in one and small-joint operations in 3. ESR was at onset mean 54 mm/h (SD 29), and at the last measurement mean 26 mm/h (SD 21). Iritis was found in 5/17 (29%); seven (41%) retired due to AS; five died.

Competing interests: none declared.

Conclusion. Our community-based inception cohorts show that with time, among a number of similarities most often sacroiliitis, peripheral arthritis and iritis developed in both chronic ReA and AS. These HLA-B27-related diseases would appear to be identical. The differences between patients depend on the chronicity of the sickness. The hypothesis that HLA-B27 is related to chronicity of disease seems to be valid.

Introduction

Ilmari Paronen mentions that arthritides following dysentery were known to Aurelianus at the beginning of the fifth century. He himself published 344 such cases in his doctoral thesis in 1948, and described in detail the clinical picture of Reiter's disease. The knee and ankle were the joints most often affected, as in earlier reports (1). Radiographs of joints in 76 cases yielded normal findings, and a shortage of film after World War II did not allow follow-up x-ray studies.

As Paronen already anticipated, the term Reiter's syndrome was subsequently abandoned and replaced by reactive arthritis (ReA) (2). Today ReA is classified as one of the spondyloarthropathies, most often presenting only in an acute form.

A prospective population-based study covering patients with recent-onset arthritis, called the Heinola Follow-up Survey of Arthritis, was initiated in 1973. We here report on the 32-35-year outcome of ReA patients, emphasizing radiographic measurements, and compared them with patients with ankylosing spondylitis (AS) followed up for twenty years.

Patients and methods

A cohort of recent-onset arthritis cases was collected at the Rheumatism Foundation Hospital in Heinola, Finland between 1973 and 1975 using the following selection criteria: age 16 years or more, swelling of at least one joint, and duration of disease not more than 6 months (3). A total of 441 patients fulfilled these criteria.

Reactive arthritis (ReA)

The diagnostic criteria for Reiter's disease were peripheral arthritis in

association with urethritis, or eye inflammation, or both, and for ReA peripheral arthritis and a recent or current intestinal or genito-urinary infection, but no symptoms of urethritis or eye inflammation (3). In 1973, antibodies for *Chlamydia* or *Campylobacter* were not yet available. A follow-up examination was arranged at 1 and 3 years from entry (3). At the 8-year follow-up in 1982 ReA (with or without Reiter's syndrome) was found in 67 patients (4). Subsequently, 4 patients with psoriasis, one not having arthritis, and 2 with bilateral sacroiliitis at onset, were excluded. A total of 50 out of the original 60 attended the 20-year follow-up, as one had died and 9 could not attend, and 40 patients attended the 32-year follow-up in November 2007 as five had died and 15 were unable to come.

Ankylosing spondylitis (AS)

The original criteria for AS were bilateral grade 2 sacroiliitis and inflammatory back pain or limitation of back mobility. These requirements were less stringent than the New York criteria. The main inclusion criterion being swollen joint, the number of AS patients at the 8-year follow-up was 22 (4). These were invited to attend the 20-year examination in 1997. Two patients with psoriasis, 2 with lumbago and no sacroiliitis, and one, who already had AS in 1962, were excluded. Of the remaining 17 patients 5 had died during 1985-95, and 3 did not attend. As AS patients already had bilateral sacroiliitis, they were not asked to attend the 32-year check-up.

The clinical history, especially the number of iritic attacks, and capacity to work were evaluated. The number of swollen joints was counted at entry and at 8-, 20- and 30-year check-ups. The 72 joints investigated were as follows: distal interphalangeal (DIP), proximal interphalangeal (PIP) of the hand and foot, metacarpophalangeal (MCP), wrist, elbow, shoulder, sternoclavicular, jaw, metatarsophalangeal (MTP), subtaloid, ankle and knee. Disability was assessed by the Health Assessment Questionnaire (HAQ) index (5) only at the 20- and 32-year check-ups. HLA-B27 typing, antibodies for *Yersinia* and

Table I. Onset age and HLA-B27 in patients with reactive arthritis and ankylosing spondylitis.

	ReA patients	ReA Male	ReA Female	AS patients	AS Male	AS Female
No. of patients (%)	60	34 (57)	26 (43)	17	7 (47)	9 (53)
Age Range	17-54	19-51	17-54	21-50	23-47	21-50
Age Mean (SD)	32 (10)	32 (9)	32 (12)	33 (10)	32 (8)	34 (11)
HLA-B27 positive (%)	51 (85)	27 (79)	24 (92)	17 (100)		

the Widal test were carried out at onset. The erythrocyte sedimentation rate (ESR) mm/h was registered at entry and at the 8-, 20-, and 30-year check-ups, and quantitative C-reactive protein (CRP) mg/l at the 8-, 20-, and 30-year check-ups. Blood haemoglobin, white blood cell count, platelets, liver enzymes, serum creatinine and urine albumin were checked at the end of follow-up. Hands, feet and sacroiliac joints were radiographed. Destruction in hands and feet was graded according to the Larsen method (6). The six grades for the MCP joints I-V and wrists and MTP joints II-V were added to form a Larsen score of 0-100. Changes in the sacroiliac joints were graded according to the revised 1984 New York classification from 0 to 4 (7).

The ethics committee of the Päijät-Häme Central Hospital accepted this study on 29.11.2006.

Results

The baseline characteristics of the patients are shown in Table I.

ReA

At entry seropositivity for *Yersinia enterocolitica* type 3 was detected in 22 patients (37%) and for *Salmonella typhimurium* in one. A recent gonococcal urethritis was found in four. Two cases of erythema nodosum were seen. One patient had carditis at entry and one later developed aortic valve insufficiency requiring pacemaker installation. Other clinical, laboratory and radiographical findings in the 60 patients during 32-35 years are shown in Table II. The onset figure for 1-5 swollen joints (65% in knee) diminished from a mean 2.6 to 1.2 at the 8-year check-up, and at the 20-year check-up only three patients had swollen joints. The number of patients with raised ESR (>24 mm/h)

diminished from initial 49/60 (82%) to 14/60 (23%) at the 8-year check-up, and thereafter to 6/50 (12%) at the 20-year, and 7/40 (18%) at the 30-year examination. Other laboratory findings were normal in the end. At the 20-year check-up cumulatively 6/60 (10%) had a Larsen score of 2-6 (mean 4). No progression was found up to the end of the study. Altogether 6 joint operations were performed. In one patient ankle joint synovectomy was performed in 1976 and later arthroplasty in 1981. One knee, and one carpal synovectomy, and 2 toe operations were made. Grade 2 or more bilateral sacroiliitis developed in 9/60 (15%), and grade 2-4 unilaterally in 3 patients. An additional 13 patients had grade 1 uni- or bilateral sacroiliitis. Iritis, in some patients recurrent, was treated in 12/60 (20%). Erosive arthritis or iritis or sacroiliitis occurred in 24/60 (40%) patients. At the end-point 13 (22%) were retired because of arthritis, and 5 (8%) had died.

AS

At the first examination AS was diagnosed in 11 patients, at the 1-3-year check-ups in 3, and subsequently in 3 patients. The 6 patients did not meet the criteria for ReA at onset. The highest ESR during the first hospitalization was 17-107 mm/h, mean 54 (SD 29). Five (29%) patients died before 1997 at the age of 39-65, mean 50 years. Their onset ESR was mean 65 mm/h (SD 28). The last ESR in all patients was 4-89 mm/h, mean 26 (SD 21), but in the deceased patients 18-89 mm/h, mean 45 (SD 31). The last CRP in all was 0-52 mg/l, mean 10 (SD 15), and in the deceased patients 0-52 mg/l, mean 18 (SD 24).

At onset 14 patients had oligoarthritis (1-4 joints) and one had 5 swollen joints. The knee joint was affected in

Table II. Outcome of 60 patients with reactive arthritis in 35 years.

Years from beginning	No. of patients	No. of swollen joints			ESR (mm/h)			CRP (mg/l)	New bilateral sacroiliitis	New cases of iritis	HAQ Mean (SD)	Retired because of arthritis	No. of operated patients	Deceased
		Range	Mean	(SD)	Range	Mean	(SD)	Mean (SD)						
0	60	1-5	2.6	(1.6)	2-123	55	(33)	ND	0	4	ND	0	1	
8	60	0-7	1.2	(1.9)	1-113	15	(17)	7 (19)	5	6	ND	1	1	
20	50	0-3	0.3	(0.8)	2-91	13	(11)	4 (6)	2	1	0.11 (0.32)	6	2	1
30	40	0-3	0.2	(0.6)	2-43	15	(11)	5 (5)	2	1	0.32 (0.47)	6	1	4
Total	60								9 (15%)	12 (20%)		13(22%)	5(8%)	5(8%)

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ND: not done.

9. One patient had at onset erosions in hand and foot, while at the end-point 5 had a Larsen score of 2-22, mean 9 (SD 8). Bilateral hip arthroplasty was performed on one patient, toe operations on two, and finger tenosynovectomy on one. One patient underwent surgery for aortic valve insufficiency and died at the age of 44 yrs. One patient had iritis once in 1969, and another 4 several times during the follow-up (29%). Four patients were retired due to AS at the 8-year follow-up, and 3 thereafter (41%). The end-point HAQ was zero in 6 patients and 0.04-0.38 in 3.

All patients did not seem to have an early disease. The history of the disease revealed that 11 had one or more symptoms years before the beginning of our study. Seven patients had had back pain (2 in childhood), 5 swollen joints (3 in childhood), 2 iritis, and one urethritis.

Discussion

At the end of World War II. there was an epidemic of dysentery in the Finnish army with a peak in 1944. In a total of 150,000 cases, ReA developed in 350 (0.2%) (1). Attack rates of 0.2-1.2% after an appropriate infection have been reported, as discussed by Savolainen *et al.* (8). The incidences of inflammatory joint diseases, ReA and AS in 1974 according to the Heinola Town Study and the present material have been estimated to be 218, 14 and 10/100,000 (10). In a more recent study from the city of Kuopio, Finland, the incidence of arthritides in the year 2000 was 271/100,000. Among adults the annual incidences of ReA and AS using strict classification criteria were 10 and 7/100,000 (8). The number of patients

in the present study was small. Since 1974 it has been sought to include all arthritic patients from a population of 260,000 (7% of the whole country) (9). If the incidence of ReA is 10/100,000, only 78 patients were to be found in that area during a period of three years.

During the years 1963-67 Sairanen *et al.* made a 20-year follow-up study of 100 of Paronen's cases (10). Thirty-two (32%) patients had sacroiliitis; out of these 8 had syndesmophytes and 7 bamboo spine, and erosion in peripheral joints in 6 cases. Iritis had appeared in 7 cases. The writers concluded that the true incidence of sacroiliitis might have been about 10-15 % in the original material (10). In 1977-79 Leirisalo *et al.* conducted a follow-up study of 313 Finnish and Danish hospital patients with ReA (11). During the acute attack 54 of the 233 (23%) investigated already had sacroiliitis. Follow-up was undertaken a mean 65 months (range 12-242) thereafter, 61/158 (39%) being found to have sacroiliitis. X-ray examination was made only during the follow-up of 66 patients. Accordingly some of Paronen's patients could have had sacroiliitis before the dysentery.

To study the present ReA cohort we excluded patients with bilateral sacroiliitis at onset. Thus we could calculate the occurrence of sacroiliitis during 35 years. It was assessed uni- or bilaterally in 20% and bilaterally in 15% of patients. These smaller figures in our inception cohort show that to investigate the true incidence of sacroiliitis in recent ReA, S-I joints should be radiographed at the outset. In the clinical situation one should avoid an x-ray load in the case of young patients with self-limiting disease. On the other

hand, sacroiliitis detected in an arthritic patient often indicates treatment with disease-modifying antirheumatic drugs (DMARDs).

We also excluded patients who later developed psoriasis. Interestingly, as far back as 1965 Khan and Hall reported seven patients out of 70 with Reiter's syndrome whose skin, nail and joint lesions progressed until the disease resembled psoriatic arthritis (PsA). Microscopic sections of skin lesions in six patients showed changes characteristic of psoriasis (12). The outcome was severe, as no DMARDs were used. Our opinion is that histology of skin or gut separates psoriatic arthritis and arthritis related to ulcerative colitis or Crohn's disease from ReA. We would abandon the principle whereby one rheumatic disease changes to another; the disease is most often the same, only doctors and criteria change.

In a rapid succession of studies in 1973 the association between HLA B27 and AS, Reiter's disease, ReA and iritis was reported (13-16). Leirisalo-Repo has recently reviewed ReA and states that while HLA B27 is not required for the development of ReA, its presence contributes to the chronicity of the disease (17). No other HLA A, B, C, DR or DQ antigen has been found to have a predisposing or protective effect in Finnish B27-negative ReA patients (18). The frequency of HLA B27 is lowest (0%) in the equatorial region and highest (40%) in northern populations. One recent hypothesis is of particular interest: HLA B27, especially subtype B2705, is disadvantageous in malaria (19). In Finland the prevalence of HLA B27 is high; the latest figure being 15.3% (20). This partly explains

the 85% prevalence of B27 in our ReA patients. Another assumption is that the mildest cases do not need hospitalization and are B27-negative.

The cause of AS has remained unknown. Sometimes the truth in medicine is simple. We remember, for example how *Chlamydia trachomatis* revealed the specific reason for non-specific urethritis. To our knowledge all follow-up studies of ReA have reported that a certain proportion of patients will have sacroiliitis and AS. Depending on the follow-up time, sacroiliitis is observed up to 49% of ReA patients (17). As we excluded patients with grade 2 sacroiliitis at onset, our figure in ReA was 15%, but the occurrence of sacroiliitis or iritis or erosive arthritis was 40%. Sacroiliitis, iritis, dactylitis or chronic arthritis, achilles tendinitis, cardiac involvement and eventually AA amyloidosis are characteristic of both chronic ReA and AS (21). In one Finnish study no major difference was found between HLA alleles in 30 patients with ReA and 30 patients with AS (22). From the clinical point of view, ReA and AS seem to be the same disease. Such a conception is by no means new. After analyzing the data of Paronen and Sairanen in 1968, Amor stated that Reiter's syndrome and AS are two aspects of the same disease (23).

Chronicity in rheumatic disease will often result in severe outcome. The frequency of HLA B27 in AS is usually 95% in Europe, higher than the over 80% in hospitalized ReA patients. If B27 has an effect on chronicity, this result is understandable. The high figure in our patients who developed sacroiliitis or iritis favours the hypothesis of chronicity.

On the basis of the literature and this inception cohort study we conclude that an essential proportion of patients with acute ReA develop objective clinical manifestations of chronicity. The worst outcome is the full picture of AS (21). Most important for the clinician today is to decide when to treat with anti-TNF agents in order to arrest this development, if the patient is not in remission (24, 25). Magnetic resonance imaging is helpful in assessing disease activity

(26). Consensus meetings dealing with this issue have taken place in different countries (27). The future calls for established diagnostic and classification criteria for this entity (28, 29). Meanwhile clinicians diagnose AS on the following criteria: bilateral sacroiliitis and inflammatory back pain or peripheral arthritis or iritis or HLA-B27. Patients with psoriasis, ulcerative colitis or Crohn's disease should be classified separately.

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