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Do infections play a role in the development of chronic inflammatory arthritis? A 14–year follow-up study of patients with early arthritis

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Abstract

Background The role of preceding infections in the development of reactive arthritis (ReA) is well known but is less studied in association with other inflammatory arthritides. Therefore, in 1979-80 we screened for infections in patients with early musculoskeletal symptoms who were referred for rheumatological consultation and assessed the role of infections and other clinical factors in the development of chronic disease in following 14 years.

Methods A total of 104 consecutive patients with suspected inflammatory musculoskeletal symptoms with a duration < 6 months were examined and screened for preceding infections in an outpatient rheumatology clinic. Follow-up evaluation was conducted after 14 years.

Results ReA, undifferentiated arthritis, and rheumatoid arthritis were the most common diagnoses at baseline and at the 14–year follow-up. Of the 80 patients participating in the 14–year follow-up evaluation, 34 (42.5%) had had evidence of infection at baseline. Twenty-four patients (30%) had developed chronic rheumatic disease. Polyarticular disease at baseline and positive rheumatoid factors predicted the development of chronic diseases. Of the patients originally diagnosed with ReA, 7.3% proceeded to ankylosing spondylitis.

Conclusion At baseline, signs of preceding infections were detected in 41% of the patients with early musculoskeletal symptoms. Preceding infections showed no association with either specific diagnosis of arthritis, except for ReA.

Clinical trial number Not applicable.

Keywords Infection, Arthritis, Reactive arthritis, Rheumatoid arthritis, Spondyloarthritis, Undifferentiated arthritis

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Introduction

The connection between infections and arthritis is multidimensional, varying from severe septic arthritis to acute or chronic reactive arthritis (ReA) or milder forms of viral arthritis [1]. Although the pathogenesis of rheumatoid arthritis (RA) is multifactorial, viruses including parvovirus B19, hepatitis C and Epstein–Barr have been associated with the development of RA [2]. Recently, an association between periodontal infections and RA has emerged [3–4]. Recent evidence has suggested an association between periodontal infections, particularly involving *Porphyromonas gingivalis*, and the development of RA due to mechanisms such as protein citrullination. ReA may develop into chronic spondyloarthritis (SpA) or ankylosing spondylitis (AS) in 10–25% of patients, *Chlamydia*-induced ReA having the worst outcome [5–6]. Prognostic factors for chronic sequelae from ReA to SpA include the type of triggering infection, HLA-B27 positivity, presence of gut inflammation, and a positive family history of SpA or AS [7].

The prognosis of RA is influenced by early diagnosis and initiation of disease-modifying antirheumatic drugs (DMARDs) [8–9]. Consequently, early referral of patients with inflammatory arthritis is recommended to enable early diagnosis and institution of early treatment to prevent joint damage and the burden of chronic disease. However, despite acute arthritis in the early phase, the symptoms may be self-limiting, especially in undifferentiated arthritis (UA) in up to 60% of cases [10]. Nevertheless, patients progressing from UA to RA should be recognized with an emphasis on early treatment.

The aim of the present study was to investigate the 14–year outcome in a group of patients referred to the university rheumatological center with suspicion of inflammatory musculoskeletal disease with duration of symptoms less than 6 months, and to assess predicting clinical factors for prolonged and chronic disease with respect to the acute diagnosis and the role of baseline infections.

Materials and methods

During 1979-80 one hundred and four consecutive patients with suspected inflammatory musculoskeletal symptoms with duration of less than 6 months were referred to the Outpatient Department of Rheumatology of Helsinki University Hospital for diagnosis and treatment. The onset of joint symptoms was defined as acute (within 7 days), subacute (2–4 weeks) or insidious (> 4 weeks). Arthritis was defined as monoarticular (one affected joint), oligoarticular (2–5 affected joints), or polyarticular (> 5 affected joints).

In addition to clinical examination, laboratory investigations included erythrocyte sedimentation rate (ESR), total blood count, kidney and liver function tests, antinuclear antibodies (upper limit of normal [ULN] 80, reciprocal titer), and rheumatoid factor (RF). To measure RF, both the Waaler-Rose (ULN 64, reciprocal titer) and latex tests (+ or –) were used. Urine was examined for leukocytes, erythrocytes, and proteins. The infections were screened as follows: antibodies against *Yersinia enterocolitica* serotypes 3 and 9 by agglutination method [11]; against *Salmonella* O antigens by Widal test; against *Chlamydia trachomatis* by the immunofluorescent antibody test. Antistreptolycin O (ASO) and teichoic acid antibodies were analyzed by radioimmunoassay methods to detect Streptococcal and Staphylococcal infections. *Mycoplasma pneumoniae* and *Toxoplasma gondii* and the following viruses: herpes simplex, varicella zoster, cytomegalovirus, adenovirus, influenza A and B, coronavirus, parainfluenza 1, 2, 3, mumps, respiratory syncytial virus, measles, rubella, polio, coxsackie virus B and rotavirus were analyzed by a complement fixation method. Serological tests for infections were repeated two weeks later to evaluate the change in the level of the titres. Tests were considered positive for yersinia with a titre of 1:320 or higher, for salmonella with a titre of 1:320 or higher, for chlamydia with a titre of ≥ 1:256 (females) and ≥ 1:128 (males). ASO was positive with ≥ 500 units and teichoic acid antibodies with ≥ 1:8. For viral infections a positive result was defined as a fourfold change in paired sera. The patients were also HLA-typed using a standard microlymphocytotoxicity test for HLA-A, -B and -DR antigens. Radiographs of the hands, feet, and lumbosacral spine were obtained when clinically indicated.

The initial diagnosis was based on the clinical features and laboratory and radiological findings. RA patients fulfilled the American Rheumatism Association 1958 revised criteria [12], AS patients fulfilled the New York 1984 criteria [13], and those with rheumatic fever fulfilled the 1965 Jones revised criteria [14]. The diagnosis of ReA and SpA was assessed according to the 1991 ESSG criteria [15]. The patients were treated according to the diagnosis. Of the original 104 patients, 92 were followed up for six months.

Fourteen years later, patients were invited to participate in a follow-up evaluation. Of the original 104 patients, five had died and 19 could not be reached or refused to participate. Thus, information on 80 patients was available for the analysis of the 14–year outcome. Investigations included HAQ (Health Assessment Questionnaire) [16], clinical and laboratory evaluations (ESR, total blood count, RF, antinuclear antibodies, and serological screening including antibodies for *B. burgdorferi* in addition to the original bacteria). Additional serum samples were collected and stored at – 20 °C. Of those samples, anti-citrullinated protein antibodies (ACPAs) were later determined using fluorometric enzyme-linked immunoassay for 64 patients. In addition to negative/

positive values (positive ≥ 7 U/ml), ACPAs were graded as low-level positive and high-level positive. Low-level positive = higher than the ULN but equal or less than three times the ULN; high-level positive = higher than three times the ULN [17]. Radiographs of the hands, feet, and lumbosacral spine were examined, if indicated. The detailed data collecting form is provided in Supplementary Information [S1].

The study was approved by the Ethics Committee of Helsinki University Hospital. Informed consent was obtained from all the participants.

The data are expressed as mean and standard deviation (SD) or count and percentage (%). Statistical comparisons between the diagnosis groups were performed with the analysis of variance (ANOVA) and Pearson's chi-square test. Multivariate logistic regression analysis with odds ratios (ORs) to assess baseline variables as risk factors for chronic disease. In the case of violation of the assumptions (e.g. non-normality) for continuous variables, a bootstrap-type method or Monte Carlo p-values (small number of observations) for categorical variables were used. Stata 17.1 (StataCorp LP, College Station, TX, USA) were used for the analysis.

Table 1 Diagnoses of all patients within first 6 months and baseline and final diagnoses of patients participating the 14-year follow-up

	All patients	Patients participating the 14-year follow-up	
	Established diagnosis within 6 months, n (%)	Established diagnosis within 6 months, n (%)	14 years, n (%)
Total number of patients	**104**	**80**	**80**
Rheumatoid arthritis	16 (15)	15 (19)	12 (15)
Undifferentiated arthritis	20 (19)	16 (20)	8 (10)
Reactive arthritis	41 (39)	31 (39)	24 (30)
Sarcoid arthropathy	3 (3)	3 (4)	1 (1)
Polymyalgia rheumatica	2 (2)	0 (0)	0 (0)
Connective tissue disease	5 (5)	3 (4)	7 (9)
Arthralgia	6 (6)	5 (6)	3 (4)
Septic arthritis	1 (1)	1 (1)	1 (1)
Ankylosing spondylitis	0 (0)	0 (0)	4 (5)
Peripheral spondyloarthritis	0 (0)	0 (0)	2 (3)
Rheumatic fever	3 (3)	2 (3)	1 (1)
Miscellaneous	7 (7)*	4 (5)**	17 (21)***

*Dermatomyositis 1, autoimmune haemolytic anaemia and nephrotic syndrome 1, rubella arthritis 1, postinfectious arthralgia 1, fever of unknown origin 1, urticaria1, enteroarthritis associated with Crohn's disease 1

** Arthrosis 2, enteroarthritis with Crohn's disease 1, rubella arthritis 1

*** Osteoarthritis 6, fibromyalgia 3, enteroarthritis with Crohn's disease 2, borreliosis 2, anti-phospholipid syndrome 2, rubella arthritis 1, fibrosing alveolitis 1

Results

Baseline characteristics and diagnoses

Of the 104 patients, 62 (59.6%) were women and the mean age was 35.6 years (SD 12.4). The onset of joint symptoms was acute in 46 (44.2%), subacute in 32 (30.8%) and insidious in 25 (24.1%) patients. Of the patients, 66 (63.5%) had large joint and 36 (34.6%) small joint involvement. The arthritis was monoarticular in 11 patients (12%), oligoarticular in 60 (65.2%) and polyarticular in 21 (22.8%). The mean ESR was 41 mm/h (SD 31.9). Nine (8.6%) were positive for RF, 33 (31.4%) for HLA-B27, 20 (19.2%) for HLA-DR1 and 18 (17.3%) for HLA-DR4.

ReA was the most common (39.4%, $N = 41$) diagnosis during the acute disease, followed by UA (19.2%, $N = 20$) and RA (15.4%, $N = 16$) (Table 1). Notably, none of the patients were diagnosed with psoriatic arthritis, gout, SpA or AS within the first six months.

Screening for any infections at the onset of joint symptoms was positive in 43 of the 104 (41.3%) patients, mostly in patients with ReA (63%). The most common trigger of ReA was *C. trachomatis* (15 patients), followed by *Yersinia* (5 patients), and *Salmonella* (2 patients).

14–year follow-up

Patient characteristics and laboratory findings

Eighty patients attended at the 14–year follow-up evaluation. The mean age of the patients was 48.8 years (SD 11.7), and 50 (62.5%) were female. The joint disease had resolved in 43 (54%) patients, while 27 (34%) had developed chronic rheumatic disease. Compared with the acute phase, there was a significant decrease in ESR (mean 40.9 mm/h, [SD 32.2] to 13.2 mm/h, [SD 13.1]) ($p < 0.001$) at the 14–year follow-up. The mean HAQ was 0.3 (SD 0.65).

Main disease groups

The baseline diagnosis was reassessed and changed in 30 patients (38% of the 80 patients participating in the follow-up, 29% of the original 104 patients). At follow-up, ReA was still the most common (30.0%, $N = 24$) diagnosis, followed by RA (15.0%, $N = 12$) and UA (10.0%, $N = 8$) (Table 1). The baseline characteristics of the patients participating in the follow-up are shown in Table 2.

Reactive arthritis

At the 14–year follow-up, 24 (30%) of the 80 participants were assessed as having had ReA. Of those with a ReA diagnosis at baseline, 31 patients participated in the 14–year visit. The original diagnosis remained unchanged in 21 patients. The other final diagnoses are presented in Fig. 1.

Table 2 Baseline characteristics, laboratory findings and diagnoses of the 80 patients participating the follow-up

	ReA *n* = 31	UA *n* = 16	RA *n* = 15	Other * *n* = 18	*P*-value
Age, years, mean (range) SD	30(9)	40(13)	40(12)	37(11)	0.010
Female, n (%)	16(52)	10(63)	13(87)	11(61)	0.19
Onset of joint symptoms, n (%)	21(68)	9 (56)	2 (14)	10 (53)	0.005
acute	8 (26)	2 (13)	4 (29)	5 (26)	
subacute	2 (6)	5 (31)	8 (57)	4 (21)	
insidious					
Size of affected joints, n (%)	8 (27)	7 (44)	6 (43)	8 (42)	0.55
small	22 (73)	9 (56)	8 (57)	11 (58)	
large					
Type of arthritis, n (%)	3(10)	1 (6)	1(7)	2(12)	< 0.001
monoarthritis	22 (76)	9 (64)	2 (13)	10 (59)	
oligoarthritis	2 (7)	3 (21)	10 (77)	5 (29)	
polyarthritis					
Back pain, n (%)	11(35)	4(25)	0(0)	2(11)	0.17
ESR mm/h, mean (SD)	53(33)	30(21)	47(28)	38(40)	0.11
RF positive, n (%)	1(3)	1(6)	5(33)	2(12)	< 0.001
HLA–B27 positive, n (%)	18(60)	4(27)	2(14)	4(22)	0.008
HLA–DR1 positive, n (%)	7(27)	4(29)	3(20)	6(40)	0.66
HLA–DR4 positive, n (%)	7(26)	5(36)	5(42)	1(6)	0.12
ASO positive, n (%)	4(13)	1(6)	2(14)	1(5)	0.77
Chlamydia antibodies positive, n (%)	10(32)	1(6)	2(14)	2(11)	0.13
Yersinia antibodies positive, n (%)	5(16)	0(0)	0(0)	0(0)	0.062
Salmonella antibodies positive, n (%)	2(7)	0(0)	0(0)	0(0)	0.66
Viral antibodies positive, n (%)	1(3)	1(6)	0(0)	3(22)	0.096
Any positivity of infection, n (%)	23(74)	6(38)	6(43)	7(39)	0.035

Percentages were calculated for positive cases of the given samples. Samples were not available of all the patients

ASO antistreptolysin O; *RA* rheumatoid arthritis; *ReA* reactive arthritis; *UA* undifferentiated arthritis

* Sarcoid arthropathy 3, connective tissue disease 3, arthralgia 5, septic arthritis 1, rheumatic fever 2, arthrosis 2, rubella arthritis 1, and enteroarthritis associated with Crohn's disease 1

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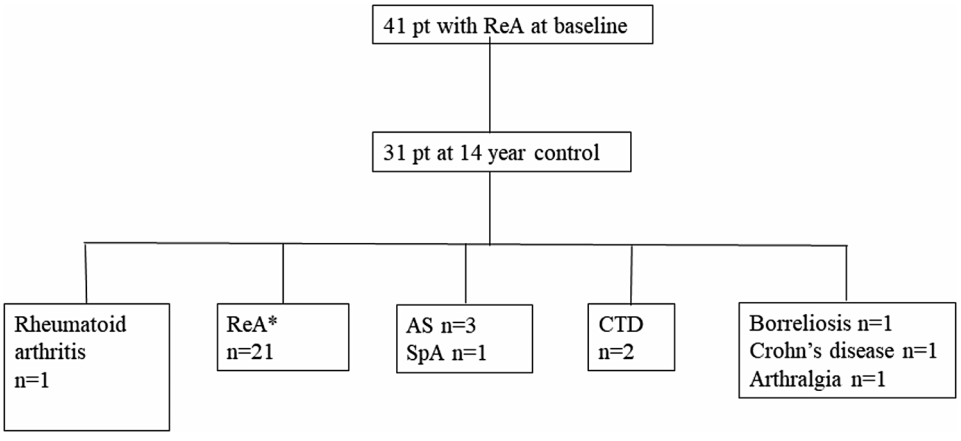

Fig. 1 Final diagnosis after 14 years of patients with reactive arthritis at 6 months. *ReA* reactive arthritis; *AS* ankylosing spondylitis; *SpA* peripheral spondyloarthritis; *CTD* connective tissue disease. *The diagnosis remained unchanged after 14 years

Although 13 (54.2%) of the patients with acute ReA as final diagnosis had recovered from the disease already during the first 6 months, six of 41 patients with ReA at baseline (14.6%) had progressed to chronic disease at the 14–year follow-up. Of these six patients with chronic disease, HLA-B27 positivity was detected in 83% (5/6) and in 53% (10/19) of those recovered ($p = 0.408$). The quality of the triggering infection in ReA did not contribute to the prognosis of ReA.

Spondyloarthritis

None of the patients had SpA or AS at baseline, but four patients were diagnosed with AS and two with peripheral SpA at the follow-up.

In the four patients with AS (two men, two women), the baseline diagnosis was UA in one patient and ReA in three patients. In two patients with ReA at baseline, one had had *Yersinia* and the other *Salmonella* infection; the one with *Yersinia* also had elevated antistreptolysin O (ASO) at baseline. Three (75%) were HLA-B27–positive. At baseline, all four patients had had peripheral arthritis, but only one had had back pain. At follow-up, all four had bilateral sacroiliitis on radiographs.

One of the two patients (male, 1; female, 1) with peripheral SpA as the final diagnosis was HLA-B27–positive. The baseline diagnosis was ReA in one and sarcoid arthropathy in the other. Both had had arthritis in the large joints (knees and ankles) at baseline and were RF-negative at baseline and at follow-up.

Rheumatoid arthritis

Fourteen of the 16 (88%) patients originally diagnosed as having RA participated in the follow-up. The diagnosis was still RA in 11 patients (69%), but in three patients it was changed (one to UA, two to CTD). In addition, the diagnosis was changed to RA in one patient with ReA as the baseline diagnosis. Diagnosis of RA was established already during the acute phase in 11 of the 12 (91.7%) patients with RA as the final diagnosis at the 14–year visit.

Of these 12 RA patients, RF was positive in five (42%) at baseline and in seven (58%) at the 14–year visit. Each of the 10 RA patients tested was ACPA-positive: seven had high-level ACPAs and three had low-level ACPAs. Furthermore, HLA-DR4 was positive in six (50%) and HLA-DR1 in two (16.7%) patients. Radiographs examined in 11 patients showed erosions and/or joint space narrowing in the hands in 10 (83%) and in the feet in nine (75%) patients. DMARDs had been started at baseline in nine (75%) patients.

Undifferentiated arthritis

Of the 20 patients with UA at baseline, the final diagnosis at follow-up was assessed in 16 patients. It remained as UA in seven patients, but changed to chronic ReA in three, to AS in one and to other rheumatological disease in five patients (osteoarthritis 3, fibromyalgia 1, antiphospholipid syndrome 1).

Of the eight patients with UA as the final diagnosis, one (12.5%) had positive ASO at baseline, but no other antibodies against bacteria or viruses, and two patients (25%) had ACPAs at a low level at follow-up. All these eight patients with UA had recovered from arthritis at follow-up.

Association between the baseline infection and the rheumatological diagnosis at the 14-year follow-up

At the onset of joint symptoms, positive screening for infections was found in 34 of 80 (42.5%) patients.

Positive infectious serology was detected in 17 (71%) of the patients with ReA, while in seven patients (2 with enteric ReA, 3 with urogenital ReA, and 2 with symptoms indicating to Reiter's syndrome) the infectious etiology of ReA remained unknown. Of the 12 patients with RA as the final diagnosis two (17%) had positive serology for *C. trachomatis* and one (8%) for *Yersinia* at baseline. One of the four patients with AS and had elevated ASO at baseline. Viral antibodies had been detected in three patients (18%) with miscellaneous diagnoses (rubella 1, herpes simplex 1, cytomegalovirus 1) and in one patient with *Chlamydia*-triggered ReA (cytomegalovirus). None of the patients with RA as final diagnosis had had a positive serology for viruses (Table 3). At follow-up, the final diagnosis was changed in two patients with recurrent borrelia arthritis according to positive antibodies against *B. burgdorferi*. The baseline diagnoses of these two patients had been seronegative RA and ReA.

Factors predicting outcome, chronic disease and work disability

Of the 80 patients participating the 14–year follow-up, the joint disease had resolved in 43 (54%) patients, while 27 (34%) had developed chronic rheumatic disease. Ten (12%) patients had experienced a new episode of joint inflammation (Table 4). Any positive laboratory evidence of infection at baseline seemed to increase the risk of chronic disease, while positive serology for solely viral infections did not (Table 5).

Of patients with poly-articular disease at baseline, 61% (11/18) had developed chronic arthritis at the 14–year follow-up, while the corresponding figures were 17% (1/6) in those with mono-articular and 20% (8/40) in those with oligo-articular disease ($p = 0.017$).

Of the eight patients with positive RF at baseline, seven (88%) had progressed to chronic arthritis ($p = 0.004$). Of the 34 patients with positive ACPAs at the 14–year follow-up, 19 (56%) had chronic arthritis ($p < 0.001$). Of those with high levels of ACPAs, seven of nine (78%) had

Table 3 Evidence of infection at baseline based on positive serology with respect to diagnosis at 14–year follow-up

Infection	ReA *n* = 24	RA *n* = 12	UA *n* = 8	CTD *n* = 7	SpA + AS *n* = 6	Other* *n* = 23	All *n* = 80
ASO, n (%)	3 (12.5)	0 (0)	1 (12.5)	3 (42.9)	1 (16.7)	0 (0)	8 (10)
Chlamydia, n (%)	10 (41.7)	2 (16.7)	0 (0)	1 (14.3)	0 (0)	2 (8.7)	15 (18.8)
Yersinia, n (%)	3 (12.5)	1 (8.3)	0 (0)	(0)0	1 (16.7)	0 (0)	5 (6.3)
Salmonella, n (%)	1 (4.2)	0 (0)	0 (0)	0 (0)**	1 (16.7)	0 (0)**	2 (2.5)
Viral ab, n (%)	1 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)**	4 (17.4)	5 (6.3)
Any positivity, n (%)	17 (70.8)	3 (25)	1 (125)	4 (57.1)	2 (33.3)	7 (30.4)	34 (42.5)

AS ankylosing spondylitis; *ASO* antistreptolysin O; *CTD* connective tissue disease; *SpA* peripheral spondyloarthritis; *RA* rheumatoid arthritis; *ReA* reactive arthritis; *UA* undifferentiated arthritis

*sarcoid arthropathy 1, arthralgia 3, septic arthritis 1, rheumatic fever 1, osteoarthritis 6, fibromyalgia 3, enteroarthritis with Crohn's disease 2, borreliosis 2, antiphospholipid syndrome 2, rubella arthritis 1, fibrosing alveolitis 1

**data of 1 patient missing

Table 4 Clinical outcome at 14-year follow-up

Baseline diagnosis	ReA *n* = 31	UA *n* = 16	RA *n* = 15	Other *n* = 18	*P*-value
Outcome					0.002
Recovered, n (%)	20(65)	10(63)	2(13)	11(61)	
Chronic disease, n (%)	6(19)	5(31)	12(80)	4 (22)	
New episode of arthritis n (%)	5(16)	1(6)	1(7)	3 (17)	
HAQ, mean (SD)	0.12(0.58)	0.29 (0.61)	0.61(0.61)	0.4 (1.0)	0.002
Diagnosis changed, n (%)	10 (32)	9 (56)	4 (27)	6 (33)	0.38

RA rheumatoid arthritis; *ReA* reactive arthritis; *UA* undifferentiated arthritis

HAQ, Health Assessment Questionnaire

Table 5 Risk factors for chronic disease

Variables	OR (95% CI)	*P*-value
Age	0.98 (0.93 to 1.4)	0.61
Sex (Male)	0.29 (0.08 to 1.05)	0.059
Any infection	3.56 (0.86 to 14.69)	0.079
Virus	0.66 (0.08 to 5.55)	0.70
Diagnosis		
ReA	1.00 (Reference)	
UA	3.18 (0.62 to 16.41)	0.17
RA	39.53 (4.82 to 79.11)	< 0.001
Other	2.37 (0.47 to 12.09)	0.30

RA rheumatoid arthritis; *ReA* reactive arthritis; *UA* undifferentiated arthritis

chronic arthritis. Of the 27 patients who tested positive for HLA-B27, 10 (37%) had chronic arthritis.

Of the 12 patients with RA as the final diagnosis, six (50%) had disability pensions, whereas none of the patients with UA as the final diagnosis had retired because of the arthritis. Disability pension had been granted to one of the 24 patients (8.3%) with ReA and to one of the four patients (25%) with AS. The presence of positive infectious serology at baseline was not significantly associated with work status (still working vs. disability pension granted).

Discussion

At the onset of joint symptoms, positive antimicrobial serology of infections was detected in 41% of the patients. Infections were most common in patients with ReA, which was the most frequent diagnosis. Our results are in agreement with a Swedish early arthritis study, in which 45% of patients had evidence of recent infection preceding the arthritis, and also there the most common diagnosis was ReA [18].

At the 14–year follow-up, 43% of the patients (34 of 80) had positive serology for the studied infections at baseline. The presence of infections was most frequent in patients with ReA but was also discovered in some patients who later developed AS or SpA. It has been suggested that infections seem to play a role in the etiology of AS, although genetic factors like HLA-B27 also influence the development of AS [19]. Of the 41 patients originally diagnosed as having ReA, three developed AS (7.3%) and one peripheral SpA. Our results are compatible with previous follow-up studies, in which 6–7% of ReA patients developed AS [20–21]. In our series, the patients with AS or SpA as the final diagnosis had UA or ReA as the baseline diagnosis and 2/3 of them were HLA-B27–positive. This is in accordance with a 10–year follow-up study of seronegative arthritis reporting 8.7% of patients reclassified as SpA and 0.7% as AS, the majority of those tested positive for HLA-B27 [22].

One quarter (3/12) of the patients with RA as final diagnosis had laboratory signs of infection at baseline, but no particular infection occurred prominently prior to RA. The preclinical phase of RA is longer, while changes in immunopathology can be seen years before the onset of symptoms [23]. Thus, the initial factors (such as infections) that initiate immunopathological changes before the onset of symptomatic RA may be difficult to discover. A large case-control study showed an association with a lower risk of RA in patients with prior gastrointestinal and urogenital tract infections and no associations with upper respiratory infections and pneumonia [24]. In contrast, a recent study found an association between

the detection rate of respiratory viral infections and an increased number of incident RA cases [25]. The association between RA and periodontitis has been investigated by several groups, who have showed a higher prevalence of *Porphyromonas gingivalis* in patients with early RA than in the control population [26–27]. This pathogen expresses peptidylarginine deiminase, an enzyme that generates citrullinated epitopes recognized by ACPAs [28].

Half of the patients recovered from rheumatic symptoms, whereas one third of the patients had developed chronic rheumatic disease. Patients with polyarticular disease at baseline had developed chronic arthritis during the 14–year follow-up significantly more often than patients with monoarticular or oligoarticular disease. This is in line with an earlier study on inflammatory polyarthritis, in which the presence of inflammation in less than six joints was among the strongest predictors of remission at two years [29].

Patients with ReA had the most favorable long-term outcomes, with more than 50% of them recovering from the arthritis. On the other hand, RA patients had the worst prognosis of all the patient groups, with a 50% disability retirement rate at the 14–year follow-up. This is of same magnitude as in a Finnish follow-up study of patients with RA from the same era and geographic area, in which the RA-related retirement rate was 39% after 15 years [30].

A considerable proportion of patients (19%) were diagnosed with UA within 6 months, whereas only 10% of patients still had this diagnosis at the 14–year follow-up. Understandably, the diagnosis was more accurate during the follow-up. In line with previous studies, the prognosis of the patients with UA as the final diagnosis was good. The diagnostic challenge of recognizing an unfavorable outcome in patients with UA has been studied in several early arthritis series [31–34], in which the transition rate from UA to RA has varied between 13% and 54%. However, the diagnosis remained UA in 21–87% of patients, and 20–60% had self-limited disease [10]. In a follow-up study, 42% of patients with UA had progressive disease after one year [31]. An Italian study confirmed that high or low levels of ACPAs increased the risk of developing RA in patients with a recent onset of UA, but the progression from UA to RA was more rapid with high levels [35]. Factors predicting persistent arthritis and poor outcomes included the duration of symptoms, older age, the presence of biomarkers (RF, ACPAs), radiological erosions, high disease activity, and a high score on the HAQ at baseline [31–32, 35–36].

The strengths of our study include the long follow-up time and the high participation rate of the study patients (77%) during the 14-year study-period. Our study has some limitations, such as the relatively small number of patients. No control population was included in the present study. However, some information exists on the prevalence of positive serology for different infections in the general population. In healthy populations, the prevalence of *Yersinia* antibodies has been 19–31% in Finland and 33–43% in Germany [37]. The prevalence of positive serology for *Salmonella enteritidis* in Finnish population was 8% when examining healthy blood donors [38]. *Chlamydia trachomatis* seroprevalence among young women (< 29 years of age) was 19.1–20.8% [39]. At the time of the baseline study, serological tests (ACPAs and antibodies against *Borrelia* or *Campylobacter*) and PCR tests (diarrhoeagenic *Escherichia coli* in stool samples) were not available. No information on smoking was gathered.

Conclusion

Signs of preceding infection were observed in 41% of the patients with early musculoskeletal symptoms, predominantly in those with ReA. Positive infectious serology at baseline was only of diagnostic use in ReA.

Abbreviations

RA	Rheumatoid arthritis
SpA	Spondyloarthritis
AS	Ankylosing spondylitis
DMARDs	Disease-modifying antirheumatic drugs
UA	Undifferentiated arthritis
ESR	Erythrocyte sedimentation rate
ULN	Upper limit of normal
RF	Rheumatoid factor
ACPAs	Anti-citrullinated protein antibodies
ASO	Antistreptolysin O
SD	Standard deviation
ORs	Odds ratios
HAQ	Health Assessment Questionnaire
CTD	Connective tissue disease

Supplementary Information

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Supplementary Material 1

Author contributions

Material preparation, data collection and analysis were performed by M.L-R, L. P, T. H, H. K, R. K and R. T. The first draft of the manuscript was written by R.T, and all the authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

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Data availability

The data of this study are available on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in compliance with the Declaration of Helsinki and its amendments. The study was approved by the Ethics Committee of Helsinki University Hospital. Informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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