Infections Preceding Early Arthritis in Southern Sweden: a Prospective Population-Based Study

MARIA K. SÖDERLIN, HANNU KAUTIAINEN, MIRJA PUOLAKKAINEN, KLAUS HEDMAN, MARIA SÖDERLUND-VENERMO, THOMAS SKOGH, and MARJATTA LEIRISALO-REPO

ABSTRACT. *Objective*. To detect evidence of infections preceding early arthritis in Southern Sweden and to compare the clinical outcome of remission during a 6-month followup for patients with and without signs of prior infection.

Methods. Adult patients with arthritis of less than 3 months' duration were referred from primary health care centers to rheumatologists. All patients were systematically screened for infections caused by *Salmonella typhimurium* and *Salmonella enteritidis, Yersinia enterocolitica, Campylobacter jejuni, Borrelia burgdorferi, Chlamydia trachomatis, Chlamydia pneumoniae,* and parvovirus B19.

Results. Seventy-one patients were included in this study. Twenty-seven (38%) patients had reactive arthritis (ReA), 17 (24%) undifferentiated arthritis, 15 (21%) rheumatoid arthritis (RA), 4 (6%) psoriatic arthritis, and the rest (11%) other diagnoses. Of all the patients, 45% had evidence of a recent infection preceding the arthritis, as indicated by laboratory tests and/or disease history. *C. jejuni* dominated the ReA group. The occurrence of recent *C. trachomatis, B. burgdorferi, C. pneumoniae,* and parvovirus B19 infections was low. Overall, 58% of the patients went into into remission during the 6-month followup. Of the patients with a preceding infection, 69% went into remission as compared to 38% of the patients without a preceding infection (p = 0.011). Thirty-three percent of the patients with RA were in remission after 6 months.

Conclusion. In this population-based cohort, 45% of the patients presenting with a new-onset arthritis had had a prior infection. *Campylobacter* ReA dominated the ReA group. There were only a few cases preceded by infections by *C. trachomatis, B. burgdorferi, C. pneumoniae,* and parvovirus B19 infections. Remission during the first 6 months was especially frequent in the group of patients with a prior infection, but the remission rate was relatively high even for arthritis without prior infection. (J Rheumatol 2003;30:459–64)

Key Indexing Terms:

| INCIDENCE | REACTIVE ARTHRITIS | CAMPYLOBACTER |
| CHLAMYDIA | | PARVOVIRUS B19 |

The diagnosis and treatment of recent-onset arthritis is challenging. Ideally, patients developing a chronic erosive disease should be identified early in order to start disease modifying treatment to prevent joint destruction and functional incapacity. Reactive arthritis (ReA) is often self-limiting with a favorable outcome. However, the prognosis of ReA is difficult to predict and varies depending on patient characteristics such as HLA-B27 status and partly on the causative agent. Most studies describing the incidence, infectious etiology, and clinical presentation of ReA have been based on selected cohorts of infected patients. Very few studies of ReA have been truly population-based.

Our aim was to determine the proportion of prior infections in patients with arthritis of less than 3 months' duration in a population-based prospective setting, and to clarify whether the clinical outcome after 6 months differed between patients with a prior infection and those without evidence of a prior infection.

MATERIALS AND METHODS

Study setting. Between May 1999 and May 2000, a prospective population-based incidence study of new referrals was conducted to establish the annual incidence of inflammatory joint diseases in the adult population of 132,000 in the County of Kronoberg in Southern Sweden[1].

The county has 2 hospitals, the Central Hospital in Växjö, and the District Hospital in Ljungby. The Rheumatology Department is located in Växjö Central Hospital. At the time of the study there was one privately practising

rheumatologist in the county, and he participated in the study. Some rheumatological patients were also treated at Ljungby District Hospital, although no rheumatologist works there. Thus, in Kronoberg County, the care of patients with active rheumatological diseases in need of specialist treatment is carried out at the Rheumatology Department in Växjö Central Hospital or by the one private practitioner participating in the study. The county has 25 primary health care centers.

Altogether, 21 primary health care centers, one private outpatient rheumatology unit, and all units at Växjö Central Hospital and Ljungby District Hospital where patients with inflammatory joint diseases might present (e.g., departments of internal medicine, orthopedics, dermatology, and infectious diseases) participated in the study. The coverage area encompassed an adult population (> 16 yrs) of 132,000 people. One of the authors (MS) visited the general practitioners in each participating primary health care center and the doctors in the participating hospital clinics in advance to inform them about the study. Quick referral to a rheumatologist in appropriate cases was particularly emphasized. In addition, all participating centers received written information. The department of orthopedics and the dermatologist at Ljungby District Hospital received only written information. Additionally, other privately practising physicians in Växjö with specialities other than rheumatology were given written information about the study before the start. At 3-month intervals, all participating primary health care centers and clinics also received a written reminder of the study, including inclusion criteria and a report of the number of included cases and the diagnoses of the patients included thus far.

Patients. Incoming patients were included in the study if they had recent-onset new joint inflammation with swelling of at least one joint, were over the age of 16 years, and if the onset of joint inflammation occurred between 1 May 1999 and 1 May 2000. Additionally, there was a time limit of 3 months from onset of symptoms to inclusion. Thus, this study represents a prospective population-based patient cohort of very early arthritis.

Children aged 16 years or less, and patients with osteoarthritis, septic arthritis, and crystal deposition diseases were excluded from the study, as were patients with a previous history of joint swelling. The general practitioners in the participating primary health care centers referred the patients either to the outpatient clinic at the Rheumatology Department at Växjö Central Hospital or to the private rheumatologist in Växjö. Some of the patients included in the study were admitted to the Rheumatology Department at Växjö Central Hospital from the emergency department of the hospital and from other clinics. Only patients residing in the County of Kronoberg were included in the study.

The patients underwent the same clinical and laboratory examinations at presentation and after 1 month, 3 months, and 6 months, or, if they recovered during the first 6 months, up to time of recovery. A chest radiograph and radiographs of involved joints were taken at presentation. All patients were interviewed as to infections preceding the onset of arthritis. The number of tender and swollen joints, patient visual analog scale (VAS) for pain and global assessment, as well as the physician assessment of overall disease activity (VAS) were recorded at each visit.

All patients with RA fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA[2]. Rheumatoid factor (RF) negative arthritis in association with psoriasis was defined as psoriatic arthritis[3]. The diagnosis of Lyme arthritis was based on a medical history of mono- or oligoarthritis with no alternative explanation, and a positive serology for *Borrelia burgdorferi* by enzyme immunoassay (EIA)[4]. ReA was defined as an inflammatory joint disease either preceded by a history of infection less than 2 months from the onset of joint symptoms and verified by cultures or positive serology, or, in the absence of a history of infection, by cultures or serology alone. Patients with arthritis with prior genitourinary infection, enteric infection, or infection in the upper respiratory tract or soft tissue were also classified as ReA. The patients with joint inflammation not fulfilling the above-mentioned criteria were classified as undifferentiated arthritis.

All the patients gave their written informed consent. The study was approved by the regional ethics committee at the University of Lund. The

patient data register was approved by the Växjö Central Hospital management committee.

Laboratory tests. Erythrocyte sedimentation rate, serum levels of C-reactive protein, blood cell count, alanine aminotransferase, serum creatinine, and urinalysis for glucose, hemoglobin and protein were taken at each visit. A stool culture, throat swab, blood samples for the HLA-B27 analysis by cytofluorometry, antinuclear antibodies by immunofluorescence microscopy, and RF by latex agglutination test were taken at presentation.

Serum antibodies to *Yersinia enterocolitica* type 3, the dominating serotype in Sweden, were determined by agglutination, and confirmed by EIA, and antibodies to *Salmonella typhimurium* and *Salmonella enteritidis* were determined by EIA[5,6]. Antibodies to *Chlamydia trachomatis* (immunotypes CJHI, GFK, and BED) and *Chlamydia pneumoniae* (strain K6) were measured by microimmunofluorescence test[7,8]. Antibodies to *B. burgdorferi*, *Campylobacter jejuni*, and parvovirus B19 were studied by EIA[4,9,10]. Parvovirus B19-IgM was measured with a commercial EIA (Biotrin, Dublin, Ireland). For further evidence of recent primary infection by parvovirus B19, the avidity of VP1-IgG and the epitope-type specificity of VP2-IgG were measured as described[11]. *C. trachomatis* DNA in first-void urine was tested by ligase chain reaction (LCx *Chlamydia trachomatis* assay, Abbott)[12]. Table 1 shows which microbiological and serological laboratory tests were taken and the time intervals for the tests. The serological tests were repeated to catch titer changes. Table 2 shows the criteria for recent and past infection.

Outcome. The study outcome up to 6 months was defined as remission according to the preliminary ACR criteria for RA patients[13]. For the patients with other diagnoses, remission was defined as the absence of swollen and tender joints.

Statistics. The remission rates between the patient groups were analyzed by chi-square test and Fisher's exact test.

RESULTS

Seventy-one patients were included in the study. The diagnoses are shown in Table 3. The group designated "other diagnoses" consisted of one case each of systemic lupus erythematosus, polymyalgia rheumatica, erosive osteoarthritis with synovitis, mixed connective tissue disease, and ankylosing spondylitis.

In 27 (38%) patients a recent infection was confirmed using microbiological techniques. Additionally, 2 patients had ReA after gastroenteritis but negative culture and serology,

Table 1. Microbiological and serological tests used in the study and the time intervals for the tests.

Test	Control		
	0 mo*	1 mo	3 mo
Serology			
Yersinia	Yes	Yes	
C. jejuni	Yes	Yes	
S. typhimurium and *S. enteritidis*	Yes	Yes	
B. burgdorferi	Yes		Yes
C. trachomatis	Yes		Yes
C. pneumoniae	Yes		Yes
Parvovirus B19	Yes		Yes
Other			
C. trachomatis DNA, first-void urine	Yes		Yes
Fecal culture	Yes		
Throat swab	Yes		

*At inclusion.

Table 2. The cutoff points for serology tests used to screen recent and past infections.

Serology Test	Recent	Past
Y. Enterocolitica	Agglutination 1:40, ELISA 100–200 E/ml	—
C. jejuni	Diffusion-in-gel EIA, IgM ≥ 5 mm, IgA ≥ 5 mm or IgG ≥ 6 mm seroconversion from negative at inclusion to positive at test, 1 mo	Diffusion-in-gel EIA, IgG ≥ 6 mm
S. typhimurium	EIA, IgM ≥ 200 AE/ml, IgA ≥ 100 AE/ml	EIA, IgG ≥ 100 AE/ml
B. burgdorferi	EIA > 2	EIA 1–2
C. trachomatis	Micro-IF test 4-fold increase of IgG/IgA titer, IgM ≥ 1:20, IgG ≥ 1:512	Micro-IF test, IgG 1:32–1:256
C. pneumoniae	Micro-IF test 4-fold increase of IgG/IgA titer, IgM ≥ 1:20, IgG ≥ 1:512	Micro-IF test, IgG 1:32–1:256
Parvovirus B19	IgM ≥ 0.251 (Biotrin EIA), IgG avidity < 15%, IgG epitope-type specificity index < 10	IgG > 0.198 (VP2-EIA), IgG 0.205 (KYVTGIN peptide EIA)

EIA:enzyme immunoassay; AE: xx; Micro-IF: immunofluorescence microscopy.

Table 3. Diagnosis and number of patients in each diagnosis group.

Diagnosis	Men	Women	Total (%)
Rheumatoid arthritis	6	9	15 (21)
Reactive arthritis	9	18	27 (38)
Psoriatic arthropathy	2	2	4 (6)
Undifferentiated arthritis	7	10	17 (24)
Sarcoid arthritis	2	0	2 (3)
Lyme arthritis	0	1	1 (1)
Other diagnoses	0	5	5 (7)
Total	26	45	71 (100)

and 3 had ReA after an upper respiratory tract infection of unknown cause. Altogether, 32 (45%) patients had an infection shortly before onset of arthritis, as verified either by positive serology and/or infection history.

Altogether, 17 (63%) of 27 patients with ReA had had a recent *C. jejuni* infection. Three patients each had evidence of 2 recent prior infections as determined by serology, one with *Y. enterocolitica* and *C. trachomatis*, one with *Salmonella* and *C. jejuni*, and the third with *Streptococcus pyogenes* and *C. jejuni*. Two patients had gastrointestinal symptoms preceding the joint inflammation, one patient had a prior urinary tract infection, and 4 had a recent upper respiratory tract infection. Two patients had a staphylococcal soft tissue infection preceding the arthritis. A total of 19 (70%) patients were classified as postenteric ReA.

Two patients fulfilling the 1987 ACR criteria for RA[2] had serologically verified recent infections, one with parvovirus B19 and the other with *C. pneumoniae*. Among the 17 patients with undifferentiated arthritis, one had a recent parvovirus B19 infection. One patient with undifferentiated arthritis had *C. trachomatis* detected in urine at the 3-month visit, but not at inclusion. Seventeen percent of the patients had serological signs of past *C. trachomatis* infection. Sixty-eight percent had IgG antibodies against *C. pneumoniae* indicating past immunity. Sixty-nine percent had past immunity for parvovirus B19.

Outcome. Seven patients either wished to discontinue the study or moved to another area, and followup data at 6 months was thus available for 64 patients (90%). During the followup period, 11 patients informed us that they were symptom-free and thus did not come for the next clinical control. These patients were regarded as in remission. In all, 37 (58%) patients were in remission within the first 6 months. Among the 32 patients with a recent infection, 22 (69%) were in remission. Among the 39 patients without a recent infection, the frequency of remission was lower, 15 (38%) (p = 0.011). Thirty-three percent of the patients with RA were in remission, including the RA patient with a prior *C. pneumoniae* infection. Fifty-seven percent of the patients with undifferentiated arthritis were in remission, as compared to 71% of the patients with ReA due to *C. jejuni*.

HLA-B27 status. A total of 13 [19% (95% CI 10-30)] patients in this study were HLA-B27 positive. Of the 27 patients with ReA, 6 [23% (95% CI 9-44)] were HLA-B27 positive. The HLA status for one patient with ReA was missing. For the patients with RA and undifferentiated arthritis, the figures were 20% (95% CI 4-48) and 18% (95% CI 4-43), respectively.

Chlamydia pneumoniae. Two patients had IgM antibodies against *C. pneumoniae*. Clinically, one was diagnosed as RA, and the other was diagnosed as ReA after an upper respiratory tract infection. The latter patient had a mild disease with synovitis in the ankle. The patient received a nonsteroidal antiinflammatory drug (NSAID) and intraarticular corticosteroid injections and was in remission at the 3-month visit. The patient with RA had aggressive arthritis and no clinical signs of previous infection. She had synovitis in metacarpophalangeal, proximal interphalangeal, and metatarsal joints, and no extraarticular features. She was treated with oral prednisolone and NSAID, and was in remission at the 6-month followup visit. Both patients were HLA-B27 negative and had no signs of internal organ involvement.

Parvovirus B19. One patient in the undifferentiated arthritis group had a serologically verified recent parvovirus B19 infection. She presented with unilateral arthritis of the ankle and unilateral wrist arthritis. Tests for HLA-B27 and RF were

negative. She declined intraarticular and oral corticosteroid treatment, but was started on methotrexate at one month because of ongoing arthritis. At 6 months she was better, yet not in remission. One patient had convalescent serology for parvovirus B19. She was clinically classified as having RA, and presented with polyarthritis of the metacarpophalangeal joints and wrists, was RF negative but HLA-B27 positive, had tendinitis at presentation, and no history of infection. She received NSAID, oral corticosteroids, and intraarticular corticosteroid injections, and started methotrexate at one month because of ongoing arthritis. She became better at 6 months with no swollen joints, but was not in remission.

Other infections. One patient had Lyme disease, with wrist arthritis resolving after 2 intraarticular corticosteroid injections and NSAID treatment. The patient with mixed connective tissue disease had positive *B. burgdorferi* serology indicating a recent infection, and she consequently received antibiotic treatment.

The stool cultures were all negative, as were all throat swabs for *S. pyogenes*.

DISCUSSION

In all, 45% of the patients in this study had an infection preceding the arthritis, indicating the importance of systematic surveillance for infections in patients presenting with early arthritis. That patients with both mild and severe arthritis could be enrolled in this study levelled out the typical referral bias, where only severe arthritis tends to be seen at the secondary center. We saw only a few patients with recent infections with *C. trachomatis*, *C. pneumoniae*, *B. burgdorferi*, and parvovirus B19. *C. jejuni* dominated the postenteric ReA group. Most of the patients with a recent infection were in remission at 6 months. However, almost 60% of the patients with undifferentiated arthritis and one-third of the RA patients were in remission. The early referral where patients were seen by a rheumatologist 3 months from the onset of symptoms enabled early therapy, which has been shown to influence the outcome of RA[14]. Twenty-five percent of the patients had undifferentiated arthritis in spite of extensive and systematic search for etiology, comparing well with earlier reports from early arthritis clinics of 20 to 56%[15].

No universally accepted criteria for ReA exist, hampering the comparison of studies. ReA is most commonly defined as arthritis after enteric infections and *C. trachomatis* urogenital infection. We also included in the ReA group arthritis with prior upper respiratory infections and soft tissue infections. In a recent article, post-test probabilities were calculated for the diagnosis of ReA[16]. We used a combination of several tests, exclusion of other diseases such as RA, sarcoidosis and Lyme disease, and IgG, IgA and IgM serology to increase the post-test probability. The frequency of HLA-B27 positivity in this patient group was somewhat higher than in the normal population in Southern Sweden, i.e., 10–12%[17].

Most epidemiological studies of postenteric ReA are done with known outbreaks of gastrointestinal infections, where the incidence rates for ReA are calculated from the arthritis patients with a known infection. In this study, all patients were tested for pathogens regardless of symptoms or history of infections. It is very difficult to establish the true number of patients with postenteric ReA in a given population, and ideally these 2 study designs should be combined.

In our study, an acute *C. pneumoniae* infection preceded one case of ReA and one RA. In 2 previous studies, *C. pneumoniae* was a triggering factor in 2.2–10% of cases with acute ReA[18-20]. The prevalence of *C. pneumoniae* IgG antibodies in our study was 68%, similar to that observed in other adult populations in the Northern hemisphere[21].

The finding of only one case of ReA preceded by *C. trachomatis* must be considered very low. Only the serology indicated a recent infection. The patient's clinical picture was suggestive of ReA (aggressive oligoarthritis) and he was HLA-B27 positive. It could be argued that positive *C. trachomatis* serology alone in a urogenitally asymptomatic patient is only suggestive for *C. trachomatis* infection, since serology for *C. trachomatis* has limited sensitivity, especially in mucosal infections; moreover, a positive antibody test is present in 10–15% of a normal population[16]. As this patient had a negative ligase chain reaction urine test and serological signs of a recent *Y. enterocolitica* infection, it might be that the *Y. enterocolitica* caused the arthritis. A study from Oslo including 186 patients with suspected ReA and recent-onset synovitis in a normal population reported a *C. trachomatis* ReA incidence of 4.6/100,000 (13%)[22]. A study of patients with a known *C. trachomatis* infection from a predominantly Afro-American population in a sexually transmitted disease clinic in Alabama reported an incidence of 4.1% for *C. trachomatis* ReA. This figure cannot be directly compared with our study, since Afro-Americans have a lower rate of HLA-B27 and this was a selected patient population of infected patients[23,24].

In our study, in which all patients were tested systematically regardless of infection history, 17 (24%) of 71 patients tested positive for a recent *C. jejuni* infection, and Campylobacter ReA dominated in the ReA group (63%). Only one patient had prior gastrointestinal symptoms. In a Swedish study with patients with a known *C. jejuni* infection, 53% of the patients had symptoms[25]. Five earlier studies of infected patient cohorts reported *C. jejuni* ReA incidence rates of 2.3–16%[25-29].

Since only 9 patients in this county were positive for Shigella during the study period, and the incidence of Shigella ReA has been reported to be only 1.5–2.5%, we did not expect to see any Shigella ReA[30,31]. That only one patient in this series had Salmonella ReA was very surprising, as we expected to see 4–18 patients, based on earlier reports of patient cohorts with positive stool cultures for Salmonella[32-38]. The reason for our small figures could be that the arthritis was mild, not necessitating a medical consultation, or that the patients were not referred to secondary care.

In our study, 2 patients (3%) had had a recent parvovirus B19 infection, a figure comparable with 2.7% from an early arthritis register[39]. Other studies report 3–6% for early RA[40-42] and 11-18% for unspecified inflammatory arthritis[40,41,43,44]. The causal relationship between a recent parvovirus B19 infection and RA is not always easy to verify as 20% of the arthritis becomes chronic and can even mimic RA[45].

We did not include a control population, as we already have information from earlier studies. There were no ongoing epidemics during the study period in Kronoberg County. During the study period, 298 patients tested positive for *C. trachomatis*, giving an incidence of 213/100,000; this corresponds to the incidence in Sweden in 2000 of 217/100,000 (data on file, Department of Microbiology, Växjö Central Hospital; and based on *Communicable Diseases in Sweden 2000*, Swedish Institute for Infectious Disease Control). The prevalence of *B. burgdorferi* seropositivity in healthy blood donors in Kronoberg County is 14% (data on file, Department of Microbiology, Växjö Central Hospital). At the time of the study, 11 patients tested positive for *Y. enterocolitica*, 124 for *C. jejuni*, 104 for Salmonella, and 9 patients for Shigella in stool cultures in Kronoberg County (data on file, Department of Microbiology, Växjö Central Hospital). The rate of recent parvovirus B19 infection in patients with recent-onset arthritis seemed to be small in the Norfolk Arthritis Register as mentioned above[39]. The prevalence of past *C. pneumoniae* immunity in this study seemed to be comparable to earlier reports with normal populations.

In this prospective referral study of very early arthritis in a population-based setting, almost half the patients had evidence of a prior infection. Most of the patients with a recent infection and undifferentiated arthritis went into remission during the first 6 months. The occurrence of recent *C. trachomatis*, *B. burgdorferi*, *C. pneumoniae*, and parvovirus B19 infections was low. *C. jejuni* dominated the postenteric ReA group.

ACKNOWLEDGMENT

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