EXTENDED REPORT

Reactive arthritis after an outbreak of *Yersinia pseudotuberculosis* serotype O:3 infection

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Ann Rheum Dis 2003;**62**:866–869

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Accepted 21 January 2003

Objective: To determine the occurrence and clinical characteristics of reactive arthritis (ReA) after an outbreak of *Yersinia pseudotuberculosis* serotype O:3 infection.

Methods: From 15 October to 6 November 1998, a widespread outbreak of *Y pseudotuberculosis* serotype O:3 occurred in Finland. A questionnaire on musculoskeletal symptoms was mailed to 38 patients with infection confirmed by culture. All patients who reported joint symptoms were interviewed by phone and their medical records of outpatient visits or hospital admission because of recent joint symptoms were reviewed.

Results: Thirty three of 38 (87%) patients returned the questionnaire. Reactive musculoskeletal symptoms were reported by 5/33 (15%): four patients (12%) fulfilled the criteria for ReA and one additional patient had reactive enthesopathy. The patients with ReA were adults (age range 40–47 years), whereas the patient with reactive enthesopathy was a 14 year old boy. In all patients with ReA, the arthritis was polyarticular. In addition to peripheral arthritis, other musculoskeletal symptoms included sacroiliitis (one patient), pain in Achilles tendon (one patient), and heel pain (two patients). HLA-B27 was positive in all the three patients tested. In three of four patients with ReA, the duration of acute arthritis was over six months.

Conclusion: *Y pseudotuberculosis* serotype O:3 infection is frequently associated with ReA and the clinical picture is severe.

Reactive arthritis (ReA) is a non-purulent joint inflammation which can be triggered by bacterial infections in the urogenital tract or in the gut, including the enteric pathogens *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*. Infections caused by *Y pseudotuberculosis* are much less common than those caused by *Y enterocolitica*[1 2] and reports of outbreaks are rare.[3]

Y enterocolitica is a well established trigger of ReA.[4] Several case reports of ReA triggered by *Y pseudotuberculosis* have been published, mostly from European countries, including Finland, France, Netherlands, and the United Kingdom,[4–17] but also from Canada.[18] In only two outbreaks caused by *Y pseudotuberculosis*, musculoskeletal complications have been followed up in larger case series.[2 3]

An outbreak of *Y pseudotuberculosis* serotype O:3 occurred recently in Finland enabling evaluation of the frequency and characteristics of reactive musculoskeletal complications in association with such an infection and confirming the severity of these complications during such an infection.

PATIENTS AND METHODS

The outbreak

A widespread food-borne outbreak of *Y pseudotuberculosis* infections occurred in Finland. From 15 October to 6 November 1998, a total of 47 cases with culture confirmed *Y pseudotuberculosis* serotype O:3 infection were identified nation wide through laboratory based surveillance. The patients ranged in age from 2 to 77 years (median 19); 25 (53%) were women and 19 (40%) were aged <15 years. Clinical microbiology laboratories forwarded bacterial isolates to the Laboratory of Enteric Pathogens at the National Public Health Institute for serotyping. Residents of two health districts in southern Finland accounted for 40 (85%) of the patients. Of these, 38 were enrolled in a population based case-control study conducted by the Department of Infectious Disease Epidemiology. The investigation implicated domestic iceberg lettuce as the vehicle for *Y pseudotuberculosis* infection.[19]

The survey on musculoskeletal symptoms

The questionnaire on musculoskeletal symptoms was sent to the 38 subjects who were enrolled in the case-control study to investigate the cause of the outbreak about four months after the onset of gastrointestinal symptoms of *Y pseudotuberculosis* infection. The questionnaire was slightly modified from that used in our earlier studies on the association of ReA with salmonella outbreaks.[20 21] It included questions about the presence, severity, and duration of diarrhoea, the presence and duration of concomitant symptoms of infection, such as abdominal pain, fever, eye, urinary and skin symptoms, painful or swollen joints, pain in tendon insertions, back pain, onset and duration of these symptoms, previous joint symptoms, eventual visits to a doctor or to a hospital because of these symptoms, and drug treatment. The questionnaire also included a graphic representation of the body on which the subject was asked to mark swollen or painful joints and tendons.

Diagnostic criteria

ReA was defined as development of synovitis (either swelling or limitation of joint movement, and pain) in a previously asymptomatic joint within the first four weeks after culture confirmed infection with *Y pseudotuberculosis* O:3. In addition, other reactive musculoskeletal complications such as signs or symptoms of inflammatory sacroiliitis, tendinitis, bursitis, or enthesopathy could be present. Each affected joint in fingers and toes was counted individually. Tendinitis, enthesopathy, and bursitis were regarded as reactive if they occurred within the first four weeks after the infection.

Patients who reported symptoms suggestive of ReA or other reactive musculoskeletal problem were interviewed by telephone (TH) to assess whether the arthritis or other musculoskeletal symptoms were associated with infection. If the subject had visited a doctor because of recent joint complaints, the patient charts were reviewed.

Table 1 Characteristics of the patients with reactive musculoskeletal symptoms

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnosis	Reactive enthesopathy	ReA	ReA	ReA	ReA
Age (years)	14	43	40	42	47
Sex	Male	Female	Male	Male	Female
Symptoms related to infection					
Diarrhoea	Yes	Yes	No	No	Yes
Abdominal pain	Yes	Yes	N.A.	Yes	Yes
Fever (≥37.5 °C)	Yes	Yes	No	Yes	Yes
Joint manifestation					
No of affected joints	28	25	27	5	22
Distribution of affected joints	MCP, DIP, and PIP of II–V fingers, knees, shoulders	MCP and PIP of II–V fingers, right wrist, knees, hips, elbows, shoulders	MTP, DIP and PIP of II–V toes, ankles, left knee	Right ankle, right knee, right shoulder, right elbow, right wrist	MTP, PIP, and DIP of right foot, knees, hips, ankles, DIP of left II finger
Thoracic/back symptom	Back and neck pain	Sacroiliitis	No	Back and neck pain	Thoracic pain
Other musculoskeletal symptoms	Achilles tendon pain, heel pain	No	Heel pain	No	No
HLA-B27	Not tested	Not tested	Positive	Positive	Positive
Duration of joint symptoms (months)	1	>6	>6	4½	>6
Visit to a doctor for joint symptoms	No	Local doctor (by phone)	Outpatient department of a hospital	Rheumatological department of a hospital	Private rheumatologist

ReA, reactive arthritis; NA, data not available; DIP, distal interphalangeal joint of hand; PIP, peripheral interphalangeal joint of hand; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint.

The ethics committee of the Helsinki University Central Hospital and of the National Public Health Institute, Helsinki, approved the study.

Statistical analysis

Data were analysed with BMDP statistical software (BMDP Statistical Software, Inc, Los Angeles, CA, USA). Proportions were compared with the χ^2 test or with Fisher's exact test. Mann-Whitney U or Student's *t* tests were used for comparisons of continuous variables. As all the participants did not answer all the items on the questionnaire, figures in "Results" are given as proportions: number with characteristic/number who answered the question.

RESULTS

All patients

Of the 38 study patients with gastrointestinal symptoms and *Y pseudotuberculosis* O:3 infection confirmed by stool culture, 33 (87%) returned the questionnaire. The mean age of the responders was 24.7 years (range 2.3–51.6); 18 (55%) were older than 16 years, and 18 (55%) were female. Thirty of 32 (94%) reported abdominal pain (the information was missing for one subject), 24/33 (73%) fever (≥37.5°C), and 15/33 (45%) diarrhoea. The median duration of diarrhoea was five days (range 1–38) and the median duration of abdominal pain 14 days (3–25).

Thirteen of 33 (39%) subjects had been admitted to hospital because of *Y pseudotuberculosis* infection, with a median duration of four days (range 2–16). Altogether, 23/33 (70%) subjects had received antimicrobial drugs, mostly fluoroquinolones.

Ocular symptoms were reported by 5/31 (16%), urinary symptoms by 2/31 (6%), and cutaneous symptoms by 5/30 (17%) subjects. Erythema nodosum was seen in one patient.

Patients with ReA

Ten of 33 subjects (30%) reported recent joint symptoms. Of these, four (12%) fulfilled the criteria for ReA and one additional patient had reactive enthesopathy. Thus, a total of 5/33 (15%) patients had reactive musculoskeletal symptoms (table 1). The remaining five subjects had other acute joint symptoms not related to the recent *Y pseudotuberculosis* infection (such as aggravation of previous joint pain, classical tension neck, and generalised myalgia).

All four patients with ReA were adults, whereas the patient with reactive enthesopathy was a 14 year old boy. Patients with ReA were older (mean 43.1 *v* 22.2; p=0.03) than those without ReA. The duration of diarrhoea or abdominal pain was not significantly different between patients with or without ReA. Two of four patients with ReA reported urinary symptoms compared with none of 29 patients without ReA (p=0.01).

In all patients with ReA, the arthritis was polyarticular with a median of 24 affected peripheral joints (range 5–27). The median interval between the onset of the first symptoms of infection and joint symptoms was 10 days (range 2–16). The most commonly affected joints were the small joints of the hands and feet, followed by knees, ankles, and shoulders. Besides peripheral arthritis, other musculoskeletal features, such as sacroiliitis (one patient) and heel pain (one patient), were seen. The patient with reactive enthesopathy reported pain in the Achilles tendon and heel pain. HLA-B27 was positive in all three patients with ReA tested.

Three out of four patients with ReA had visited a doctor because of arthritis, and the fourth patient had contacted a local doctor by telephone. The joint symptoms in two of the patients with ReA were sufficiently severe to lead to admission to hospital. In three of four (75%) patients with ReA, the duration of acute arthritis was more than six months. None of the four patients with ReA had a history of previous joint disease.

DISCUSSION

In our study, the incidence of ReA after an outbreak of *Y pseudotuberculosis* serotype O:3 infection was 12%. Because one additional patient had reactive enthesopathy, some 15% of patients had reactive musculoskeletal symptoms. Although this is slightly less than the 21% in a previous study of an outbreak with *Y pseudotuberculosis* serotype O:3 infection,[3] it confirms the high frequency of ReA after this infection. Both are higher than the 3% frequency (only one patient) reported after an outbreak of *Y pseudotuberculosis* serotype O:1a infection.[2] The incidence of ReA appears to be higher in *Y pseudotuberculosis* serotype O:3 outbreaks than in *Y pseudotuberculosis* serotype O:1 outbreaks (table 2). However, as ReA is considered less common in children than in adults,[22–25] it is possible that the different age distributions in the reported outbreaks might have influenced the observed incidences of

Table 2 Published follow up studies of rheumatological symptoms after *Yersinia pseudotuberculosis* outbreaks

	Tertti *et al* 1984	Tertti *et al* 1989	Present study
Serotype of *Y pseudotuberculosis*	O:3	O:1a	O:3
No of patients in the outbreak/evaluated for ReA	19/19 (100%)	50/34 (68%)	47/38 (81%)
Diagnosis of *Y pseudotuberculosis*: culture/serology	12 Culture 7 Serology	5 Culture 29 Serology	All culture confirmed
Age, mean (range)	23 (5–75)	9 (7–15)	25 (2–52)
Sex, F/M	9/10	NM	18/15
Patients with ReA			
No (%) of patients with ReA	4/19 (21)	1/34 (3)	4/33* (12)
Age, mean (range)	20 (8–23)	12	43 (40–47)
Sex, F/M	1/3	0/1	2/2
Distribution of affected joints	"Severe synovitis of several joints"	Right ankle, right toes, left knee	Polyarticular (see table 1 for detail)
Positive HLA-B27	3/4	1/1	3/3†

NM, data not mentioned in the study
*Data available for 33/39 patients; †NA in one patient.

ReA. All our four patients with ReA were adults, whereas in the previous study of infection with *Y pseudotuberculosis* serotype O:3, two of the four patients with ReA were less than 16 years old,[3] and in another study by Tertti *et al* infection with *Y pseudotuberculosis* serotype O:1a, the study group comprised only children under 16 years old, and only one child, a 12 year old boy, had ReA.[2]

Differences in the occurrence of ReA may be explained by the varying arthritogenic potential of different *Y pseudotuberculosis* serotypes, differences in case ascertainment, and definitions used for *Y pseudotuberculosis* infection in the outbreaks, as well as different definitions of ReA (table 2). The limited number of patients in the reported outbreaks may also have a role. In our study ReA was severe in most cases. Three out of four patients had visited a doctor and two of them had been admitted to hospital because of arthritis. In addition, ReA ran a prolonged course (the duration of acute arthritis was more than six months) in three of our four patients. In the previous study of an outbreak of *Y pseudotuberculosis* serotype O:3,[3] the duration of acute arthritis was not reported. However, in the follow up study of this outbreak 10 years later, two patients with initial ReA had developed ankylosing spondylitis and five patients chronic arthralgia or back pain.[1] In previous reports an occasional duration of acute arthritis for more than six months has also been seen.[5 7 8 11 18]

The association between ReA and HLA-B27 is well known. In our four patients with ReA, HLA-B27 was positive in all the three patients tested. In the earlier outbreak of *Y pseudotuberculosis* serotype O:3,[3] three of the four patients with ReA were HLA-B27 positive.

The arthritis was polyarticular (when each affected joint in fingers and toes was counted individually) with a predominance of small joints of the hands and feet. In one of our patients with ReA, we observed also clinical sacroiliitis as seen previously in occasional cases.[10 14 17] As other musculoskeletal complications, heel pain occurred in two of our patients and Achilles tendinitis in one. Previously, these manifestations have been reported not infrequently in case reports.[10 11 15–18]

In conclusion, ReA occurred in 12% of our patients, all adults. The clinical picture of acute arthritis was severe with a prolonged course over six months in the majority of the patients. *Y pseudotuberculosis* O:3 infection is associated with a high incidence and severe form of ReA.

ACKNOWLEDGEMENTS

The authors express warmest thanks to Eija Kela and Saija Hallavuo for their assistance in the investigation.

The study was supported by grants from Helsinki University Central Hospital Research Funds and Clinical Research Institute of Helsinki University Central Hospital.

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