EXTENDED REPORT

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

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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* and reports of outbreaks are rare.1

*Y. enterocolitica* is a well-established trigger of ReA.2 Several case reports of ReA triggered by *Y. pseudotuberculosis* have been published, mostly from European countries, including Finland, France, Netherlands, and the United Kingdom,3,4 but also from Canada.5 In only two outbreaks caused by *Y. pseudotuberculosis*, musculoskeletal complications have been followed up in larger case series.6,7

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.8

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.9,10 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 sacroilitis, 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.
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 \( \chi^2 \) 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 in one subject), 24/33 (73%) fever (\( >37.5^\circC \)), 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 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 sacroilitis (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,\(^1\) 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,\(^1,2,25\) it is possible that the different age distributions in the reported outbreaks might have influenced the observed incidences of

<table>
<thead>
<tr>
<th>Joint manifestation</th>
<th>No of affected joints</th>
<th>Distribution of affected joints</th>
<th>Thoracic/back symptom</th>
<th>Other musculoskeletal symptoms</th>
<th>HLA-B27</th>
<th>Duration of joint symptoms [months]</th>
<th>Visit to a doctor for joint symptoms</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP, DIP, and PIP of II–V fingers, knees, shoulders</td>
<td>28</td>
<td>MCP and PIP of II–V fingers, right wrist, knee, hips, elbows, shoulders</td>
<td>Sacroilitis</td>
<td>Achilles tendon pain, heel pain</td>
<td>Not tested</td>
<td>1</td>
<td>No</td>
<td>Reactive enthesopathy</td>
</tr>
<tr>
<td>MTP, DIP and PIP of II–V toes, ankles, left knee, right shoulder, right elbow, right wrist</td>
<td>25</td>
<td>Right ankle, right knee, right shoulder, right elbow, right wrist</td>
<td>No</td>
<td>Heel pain</td>
<td>Not tested</td>
<td>&gt;6</td>
<td>Local doctor (by phone)</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>MTP, PIP, and DIP of right foot, knees, hips, ankles, DIP of left II</td>
<td>27</td>
<td>Left ankle, right knee, left shoulder, left elbow, left wrist</td>
<td>No</td>
<td>Back and neck pain</td>
<td>Positive</td>
<td>&gt;6</td>
<td>Outpatient department of a hospital</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>MTP, PIP, and DIP of right foot, knees, hips, ankles, DIP of left II</td>
<td>5</td>
<td>Right ankle, right knee, left shoulder, left elbow, left wrist</td>
<td>No</td>
<td>Thoracic pain</td>
<td>Positive</td>
<td>&gt;6</td>
<td>Rheumatological department of a hospital</td>
<td>Reactive arthritis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Reactive arthritis</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of the patients with reactive musculoskeletal symptoms

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.
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, 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.

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 over six months in the majority of the patients tested. In the earlier outbreak of ReA there were 19 patients in total, whereas in our study 34 patients were evaluated for ReA. All culture confirmed patients with initial ReA had developed ankylosing spondylitis and five out of six patients had chronic enthesitis.

The association between ReA and HLA-B27 is well known. In our study all the patients had HLA-B27 positive. In the previous reports of ReA after *Y. pseudotuberculosis* infection in children, one of the four patients with ReA had HLA-B27 positive.

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.

<table>
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<th>Table 2 Published follow up studies of rheumatological symptoms after <em>Yersinia pseudotuberculosis</em> outbreaks</th>
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<tr>
<td>Serotype of <em>Y. pseudotuberculosis</em></td>
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<tr>
<td>-------------------------------------</td>
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<tr>
<td>No of patients in the outbreak/evaluated for ReA</td>
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<tr>
<td>Diagnosis of <em>Y. pseudotuberculosis</em>: culture/serology</td>
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<td>Age, mean (range)</td>
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<td>Sex, F/M</td>
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<td>Patients with ReA</td>
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<td>No (%) of patients with ReA</td>
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<tr>
<td>Sex, F/M</td>
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<tr>
<td>Distribution of affected joints</td>
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<td>Positive HLA-B27</td>
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NM, data not mentioned in the study
*Data available for 33/39 patients; TNA in one patient.

**ACKNOWLEDGEMENTS**
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**REFERENCES**

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