Reactive arthritis following an outbreak of *Salmonella typhimurium* phage type 193 infection

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**Objectives:** To determine the occurrence and the clinical picture of reactive arthritis (ReA) following an outbreak of *Salmonella typhimurium*.

**Methods:** An outbreak of *S typhimurium* phage type DT 193 occurred in several municipalities in Finland in 1999. A questionnaire which had a specific emphasis on musculoskeletal symptoms was mailed to all 78 subjects with a positive stool culture. Based on the answers, all subjects with recent joint complaints were clinically examined or interviewed by telephone.

**Results:** Sixty-three of 78 subjects (81%) returned the questionnaire. Of these 63 subjects, five (8%) fulfilled the criteria for ReA. All the five subjects with ReA were adults with oligo- or polyarthritis. The antigen HLA-B27 was positive in two of the four subjects tested. In two of five subjects with ReA, the duration of acute arthritis was over six months. Subjects who had received antimicrobial drugs developed acute musculoskeletal symptoms significantly (p=0.013) less often than those without such treatment. None of the subjects with ReA had received antimicrobial drugs before the onset of joint symptoms.

**Conclusions:** The occurrence of ReA following an outbreak of *S typhimurium* was at the same level as in outbreaks due to other salmonella serotypes reported previously by us, indicating that the frequency of ReA after various outbreaks is ~10%. Early use of antimicrobial drugs may prevent the development of musculoskeletal symptoms.

**SUBJECTS AND METHODS**

The outbreak

An outbreak of acute gastrointestinal infection caused by a rare definite phage type DT 193 of *S typhimurium* occurred in several municipalities in Finland in the spring of 1999. In all, 78 subjects were verified to have infection caused by this phage type. The origin of the outbreak was unknown.

**Questionnaire on musculoskeletal symptoms**

The questionnaire was sent to all 78 subjects with a positive stool culture. The mailing was carried out within two months after the outbreak was noticed. Two separate reminders were sent to those who did not respond. The questionnaire was analogous to that used in our earlier studies dealing with ReA in association with other salmonella outbreaks. In addition, we focused more specifically on the onset and duration of diarrhoea and of musculoskeletal symptoms in order to examine the effect of antimicrobial treatment of diarrhoea on the occurrence of musculoskeletal systems.

**Diagnostic criteria**

ReA was defined as the development of synovitis (both swelling and pain) in a previously asymptomatic joint within the first weeks after a gastrointestinal infection; there could also be signs or symptoms of inflammatory low back pain, tendinitis, enthesopathy, or bursitis. Each affected joint in toes and fingers was counted individually. Any other forms of joint or back pain during or after the acute infection were also recorded.

**Clinical examination**

From the answers to the questionnaire, all subjects with suspected ReA or other reactive musculoskeletal manifestations were invited to attend a clinical examination performed by the study rheumatologist (TH). Blood was collected for the measurement of erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, and for HLA-B27 analysis at the clinical examination, which was performed a median of six months after the onset of musculoskeletal manifestations. If the subject could not attend for the clinical examination, the musculoskeletal diagnosis was based on interview by telephone or solely on the information obtained by the questionnaire.

**Statistical analysis**

Data were analysed by the BMDP statistical software system (BMDP Statistical Software, Inc, Los Angeles, CA, USA). Proportional data were compared by the x² test or with Fisher’s exact test. The Mann-Whitney U or Student’s t tests were applied for comparisons of continuous variables. Statistical significance was set at the 5% level.

**Abbreviations:** ReA, reactive arthritis
the onset of diarrhoea except in subject 24, where it was the day of
26/32 subjects who received antimicrobial drugs. Day 0 = day of
(81%) abdominal pain, and 45/58 (78%) fever (>37.5°C). Of the 78
subjects, 63 (81%) returned the questionnaire. The
All subjects
Of the 78 subjects, 63 (81%) returned the questionnaire. The
median age of responders was 30.7 years (range 2–66), 50
(79%) were older than 16 years, and 37 (59%) were women. As
features of infection, 54/63 (86%) reported diarrhoea, 51/63
(79%) had acute postinfective arthritis or lumbar pain. Further-
more, five subjects (8%) had joint or back pain in association
with acute salmonella enteritis. The remaining three subjects
had other coexistent joint symptoms not related to the recent
salmonella infection (tension neck, distension of ankle, arthralgia due to concurrent hepatitis B infection).

**Subjects with ReA**

The five subjects with ReA were all adults (three women, two
men) with a median age of 34.8 years (range 30–46). The
median onset of joint symptoms was two days (range 1–9)
after the first symptoms of diarrhoea (or positive stool sample
in one subject). The arthritis was oligoarticular in three and
polyarticular in two subjects. Besides peripheral arthritis, two
subjects had inflammatory low back pain; each of these two
subjects also had Achilles tendinitis, and one of them
enthesopathy.

All five subjects with ReA had visited a doctor because of
arthritis, and two subjects had acute arthritis severe enough to
lead to admission to hospital. The joint symptoms lasted from
two to three months in three subjects and over six months in
two subjects. Two of the four tested subjects with ReA were
positive for HLA-B27. The duration and severity of joint symp-
toms were much the same, irrespective of the HLA-B27 status.

**Antimicrobial treatment**

Altogether, 32/63 (51%) subjects had received antimicrobial
drugs, exclusively fluoroquinolones, for intestinal or extraintestinal symptoms (fig 1). The causative salmonella strain
was sensitive to ciprofloxacin. The average interval time
between the onset of diarrhoea (or positive stool sample in one
subject who had no gastrointestinal symptoms) and the onset
of antibiotic treatment, and the average duration of antibiotic
treatment did not differ significantly between subjects with or
without musculoskeletal complaints (9.0 v 9.1 days, and 11 v
10 days, respectively). Of the 25 subjects with acute musculo-
skeletal symptoms, 22 provided detailed information which
enabled us to analyse the association between the anti-
microbial treatment and the occurrence of musculoskeletal
symptoms. Of these 22 subjects, two had received anti-
microbial drugs before the onset of joint complaints, whereas
13/31 subjects who had no musculoskeletal symptoms had
received antimicrobial chemotherapy (9% v 42%; p=0.013). In
the ReA group (n=5) none had received antimicrobial drugs
before the onset of joint disease, whereas in the rest of the
subjects who provided sufficient information (n=57), 26 sub-
jects had received antimicrobial drugs (0% v 16%; p=0.056).
No distinct time interval existed within which early interven-
tion with antibiotics would have prevented the development
of musculoskeletal symptoms (fig 1).

**Table 1**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Serovar</th>
<th>Source</th>
<th>Number of subjects in the outbreak</th>
<th>Snake type</th>
<th>No (%) of subjects who responded to the questionnaire</th>
<th>Number of patients with ReA</th>
<th>Occurrence of ReA† (% (No))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathila et al, 1994 [8]</td>
<td>4,5,12.b-</td>
<td>Mung bean sprouts</td>
<td>272</td>
<td>QwCE</td>
<td>246 (90)</td>
<td>17</td>
<td>6.9 (17/246)</td>
</tr>
<tr>
<td>Present study</td>
<td>Typhimurium</td>
<td>Food</td>
<td>78</td>
<td>QwCE</td>
<td>63 (81)</td>
<td>5</td>
<td>7.9 (5/63)</td>
</tr>
</tbody>
</table>

*Based on studies with a reliable estimate of the total number of infected subjects; †presented as calculated in the referred study; ‡number of subjects admitted to hospital for salmonellosis; §number of subjects with adequate data; ¶number of subjects with positive stool culture for salmonella.

NA, data not available; H, hospital based; QwCE, based on questionnaire followed by clinical examination; G, based only on questionnaire.
DISCUSSION

For other salmonella outbreaks, in which the size of the epidemic has been adequately estimated, the incidence of ReA varied between 1.2% and 15% (table 1). In our study the occurrence of ReA was 8%. This incidence is compatible with our two earlier studies, in which the occurrence of ReA was 11.5% and 6.9% with the serotypes 4,5,12:b- and Bovismorbi-

ficans, respectively. As we have applied the same methodology in our studies, these observed incidences seem to be reliable and valid. The response rate to the questionnaire has been high, between 81% and 91%, and the diagnostic criteria for ReA has been the same in all our studies. Based on the current study and our previous series, arthritogenicity of the triggering salmonella infections is quite similar, irrespective of the specific serotype.

According to our results, antimicrobial chemotherapy seems to have an impact on the development of acute musculoskeletal symptoms following salmonellosis. To date, unlike gastrointestinal infection, a positive effect of the early use of antimicrobial drugs on the prevention of ReA has been seen only in acute non-gonococcal urethritis. This has been evaluated previously in two studies of salmonella outbreak, but neither study showed that early antibiotic treatment was efficacious. As a modification to our previous study, the use of antibiotic treatment was particularly examined in the present study.

Two recent studies showed that ciprofloxacin had no advantage over placebo on the outcome of acute enteric ReA. The object of these studies, however, was to evaluate the use of antimicrobial drugs in the treatment of ReA rather than in the prevention of it. As prospective controlled studies to assess the effects of antimicrobial drugs in the prevention of ReA in humans are difficult to perform, investigations relying on retrospective analysis of defined study groups are the only clear possibility. This was also the situation in the aforementioned study of Bardin et al. According to an experimental animal model, the early use of antimicrobial drugs in the prevention of enteric ReA, is not unreasonable: an early course of ciprofloxacin before the appearance of any signs of arthritis prevented ReA, whereas antibiotic treatment of fully developed arthritis was not effective.

In summary, our study has two important implications. Firstly, the arthritogenicity of the salmonella infections seems to be quite similar, irrespective of the triggering serotype. Secondly, early use of antimicrobial chemotherapy may be effective in preventing the development of acute musculoskeletal symptoms following salmonellosis. Despite this encouraging result the role of antimicrobial drugs in the prevention of ReA triggered by enteric infection is still unsettled and warrants future studies.

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