EXTENDED REPORT

Reactive arthritis attributable to *Shigella* infection: a clinical and epidemiological nationwide study

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Objective: To study the incidence and clinical picture of *Shigella* associated reactive arthritis (ReA) and the arthritogenicity of various *Shigella* species in the population.

Methods: A questionnaire on enteric and extraintestinal, especially musculoskeletal, symptoms was sent to 278 consecutive patients with *Shigella* positive stool culture and to 597 controls. Analysis of self reported musculoskeletal symptoms was supplemented with clinical examination of those subjects with recent symptoms.

Results: Of the patients, 14/211 (7%) had ReA, and a further 4/211 (2%) other reactive musculoskeletal symptoms. Of the 14 patients with ReA, 10 had *S sonnei*, three *S flexneri*, and one *S dysenteriae* infection. HLA-B27 was positive in 36% of the patients with ReA. One control subject had ReA. In the patients with *Shigella* infection, the odds ratio for developing ReA was 16.2 (95% confidence interval 2.1 to 123.9), p = 0.001.

Conclusions: ReA occurred in 7% of patients after *Shigella* infection, with an annual incidence of 1.3/1 000 000 in Finland. Besides *S flexneri*, *S sonnei* and *S dysenteriae* can also trigger ReA.

The genus *Shigella* comprises four species: *S dysenteriae*, *S flexneri*, *S boydii*, and *S sonnei*. In developing countries in general, the most common serogroups are *S flexneri*, *S boydii*, and *S dysenteriae*, whereas in developed countries, the most common is *S sonnei* and the least common *S dysenteriae*.1, 2

In Finland, with a population of 5.2 million, the annual number of bacteriologically verified reports *Shigella* cases, according to the National Infectious Disease Registry (National Public Health Institute [KTL], Helsinki), has varied in recent years between about 50 and 100. About 90% of these infections are imported. The majority, about 60%, of all *Shigella* cases are caused by *S sonnei*, followed by *S flexneri*, *S boydii*, and *S dysenteriae* (Statistics of the Laboratory of Enteric Pathogens, KTL).

Extraintestinal complications in patients with *Shigella* infection include erythema nodosum, conjunctivitis, and reactive arthritis (ReA). ReA is a non-purulent joint inflammation, which can be triggered by infections in the gut or urogenital tract. Most ReA cases specifying the triggering *Shigella* species are due to *S flexneri*, but *S sonnei* has been reported in a few cases.3-5 One case report also exists in which the triggering species was *S dysenteriae*.6

In medical reports published in English, the few rheumatological surveys on *Shigella* outbreaks show occurrences of ReA of between 1.5% and 4%, and 4-8 but no large population based study of the incidence of *Shigella* triggered ReA has been performed. Our study aimed at examining the incidence and clinical picture of ReA and other reactive musculoskeletal symptoms in patients with positive stool culture for *Shigella*, the arthritogenicity of various *Shigella* species, and the frequency of such symptoms also in controls matched for age and sex.

PATIENTS AND METHODS

Study design

Between October 1996 and September 2000, a questionnaire on enteric and extraintestinal symptoms was sent to consecutive subjects with a *Shigella* positive stool culture. The questionnaire also went to controls matched for age, sex, and municipality recruited from the Finnish Population Registry. If no response was obtained from a control within 2 weeks, the questionnaire was sent to another matched control. Altogether, the questionnaire was posted to a total of 278 subjects with *Shigella* infection and to 597 controls. *Shigella* findings were submitted from the local microbiology laboratories to the Laboratory of Enteric Pathogens of KTL, the reference laboratory for the whole of Finland, where all *Shigella* findings are verified. In addition to *Shigella*, all stool specimens were cultured in the local microbiology laboratories also for *Salmonella*, *Campylobacter*, and *Yersinia* species, but, unfortunately, we had no access to these local data. Of the 278 *Shigella* positive subjects and 597 controls, 211 (76%) and 330 (53%), respectively, returned the questionnaire, based on which, 190 matched case-control pairs were formed for comparison of musculoskeletal symptoms between *Shigella* positive patients and those of controls. The study protocol was approved by the ethics committees of the Helsinki University Central Hospital (HUCH) and of the KTL, Helsinki.

*Shigella* strains

Identification of all *Shigella* strains was confirmed by standard methods.1

Questionnaire

The questionnaire covered the presence, severity, and duration of diarrhoea; the presence of concomitant symptoms of infection, such as abdominal pain, fever, eye symptoms, skin and urinary symptoms; painful or swollen joints; limitation of joint movement; pain in tendon insertions; low back or neck pain; time of onset and duration of these symptoms; eventual visits to a physician or admittances to hospital and drug treatment for these symptoms during the preceding 6 months; and previous joint or other musculoskeletal complaints or diagnoses. The questionnaire included a graphic representation of the body on which each symptom was depicted.

Abbreviations: CI, confidence interval; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; ReA, reactive arthritis; ReTEB, reactive tendonitis, enthesopathy, or bursitis; RF, rheumatoid factor.
subject was asked to mark the swollen or painful joints and tendons. Both the patients and controls received analogous questionnaires. The questionnaire was the same used in our earlier study dealing with ReA attributable to Campylobacter in the population.\textsuperscript{11}

### Diagnostic criteria

Information on the travel history of a patient came from the form that accompanied a Shigella strain submitted to the Laboratory of Enteric Pathogens. The strain was defined as domestic if it was isolated from a patient with no travel history within the month preceding the sampling or without contact with any person returning from abroad and suffering from shigellosis.

ReA was defined as the development of synovitis (either swelling or limitation of joint movement, and pain) in a previously asymptomatic joint, or as inflammatory low back pain (low back pain worse by night) within the first 2 months after a gastrointestinal infection.\textsuperscript{12} For patients with a positive history of chronic rheumatic disease, any new acute arthritis or acute lumbosacral pain was regarded as evidence of ReA. For synovitis, we accepted either the findings of the clinical examination or the description given in the questionnaire. Each affected joint in the fingers and toes was counted individually. Tendonitis, enthesopathy, and bursitis were regarded as reactive if occurring within the first 2 months after a gastrointestinal infection.\textsuperscript{12} For patients with a positive history of chronic rheumatic disease, any new acute arthritis or acute lumbosacral pain was regarded as evidence of ReA. For synovitis, we accepted either the findings of the clinical examination or the description given in the questionnaire. Each affected joint in the fingers and toes was counted individually. Tendonitis, enthesopathy, and bursitis were regarded as reactive if occurring within the first 2 months after the infection. Any other forms of joint or back pain during or after the acute infection were also recorded. The appropriate musculoskeletal diagnosis given to all patients and control subjects was based on information from the questionnaire, completed with data from a clinical examination if performed.

### Clinical examination

All subjects reporting recent joint complaints (79 in the Shigella positive and 81 in the control group) were invited for a clinical examination by study rheumatologists (TH, M L-R) at the Outpatient Department of Medicine, HUCH. The clinical examination was performed on Shigella patients within a median of 13 weeks (range 3–40) after the date of the positive stool specimen, and on controls within a median of 11 weeks (range 3–20) after the return of the questionnaire. A detailed study of affected joints and tendons was an essential part of the clinical examination, which was performed without knowledge of the Shigella species. In addition, blood was collected for measurement of erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and rheumatoid factor (RF), and for antigen HLA-B27 analysis.

### Statistical analysis

Proportional data were compared with the $\chi^2$ test or with Fisher’s exact test. The Mann-Whitney U test or Student’s $t$ test was applied in comparisons of continuous variables. Analysis of case-control pairs was by paired sample $t$ test and McNemar’s test. For associations between musculoskeletal diagnoses and exposure (Shigella infection) in these case-control pairs, odds ratios (OR) with 95% confidence intervals (95% CI) were computed. Differences at the 5% level were considered statistically significant. Data were analysed by SPSS statistical software version 10.05 (SPSS, Inc, Chicago, IL, USA).

As all subjects did not answer all the items on the questionnaire, figures in the “Results” are, if necessary, given as proportions of positive answers/number of responders.

### RESULTS

#### Shigella positive patients

The mean age of the 211 Shigella positive patients was 37.8 years (range 2–76). Of these, 11 (5%) were younger than 16, and 133 (63%) were female. As symptoms of Shigella infection, 210/211 (99.5%) reported diarrhoea, 166/204 (81%) abdominal pain, and 156/203 (77%) fever ($>37.5^\circ$). A total of 90% of the Shigella cases were known to be associated with travelling abroad.

In the 211 Shigella positive patients, stool culture was positive for S sonnet in 161 (76%), for S flexneri in 36 (17%), for S boydii in 9 (4%), and for S dysenteriae in 5 (2%) (Fig 1).

#### Reactive musculoskeletal symptoms

Recent joint or other musculoskeletal symptoms were reported by 79/204 (39%) Shigella positive patients and by 81/325 (25%) controls ($p<0.0001$). Of these 79 Shigella positive patients and 81 controls, 35 (44%) and 18 (22%), respectively, were clinically examined. Of the 211 patients with Shigella infection, 14 patients (7%) fulfilled the criteria for ReA and an additional 4 (2%) for reactive tendinitis, enthesopathy, or bursitis (ReTEB). Thus, of the Shigella patients, 18 (8.5%) who were clinically examined, all adults, showed reactive musculoskeletal symptoms. (In addition, one patient described symptoms suggestive of ReA and one other patient of ReTEB on the questionnaire, but neither participated in the clinical examination; adding these
patients to the calculations would have increased the ReA frequency to 7.1% and of all the reactive musculoskeletal symptoms to 9.5%.) Based on clinical examination and/or questionnaire, 1/330 (0.3%) in the control group had symptoms suggestive of acute ReA attributable to urological infection.

Among *Shigella* positive patients, those 18 with reactive musculoskeletal symptoms had a significantly higher prevalence of ocular symptoms (18% v 6%; *p* = 0.023), but not of urinary (9% v 7%; *p* = 0.748) or of skin symptoms (9% v 8%; *p* = 1.0) than patients without reactive symptoms (*n* = 193). No significant differences related to sex or to age distribution were found between these two groups (data not shown), although the former group (mean (SD) 43.6 (13.6) years) tended to be older (37.2 (14.1); *p* = 0.67). The duration of diarrhoea, fever or abdominal pain also did not differ significantly between these two groups (data not shown).

### Patients with *Shigella* triggered ReA

Among the 14 patients with ReA, the *Shigella* infection was imported in all (one each from the Baltic countries, Nigeria, Thailand, and Dominican Republic). Of these patients with ReTEB (table 1), three had a positive stool culture for *S* sonnei and one for *S* dysenteriae. Two patients with ReTEB had visited a physician for their musculoskeletal complaints. The duration of acute ReTEB could be determined in only one patient; it was 1–2 months.

### Laboratory findings for patients with ReA and ReTEB at the clinical examination

The prevalence of HLA-B27 was 36% (5/14) among patients with ReA, including two patients with pre-existing ankylosing spondylitis. In these patients with ReA, the prevalence of HLA-B27 was 3/10 (30%) with *S* sonnei, 2/3 (67%) with *S* flexneri, and 0 with *S* dysenteriae (*p* = 0.331; *χ²* test). None of the patients in the ReTEB group were HLA-B27 positive. In the patients with ReA, the presence of the HLA-B27 antigen had no statistically significant effect on the duration of ReA or on the size of the joints affected (data not shown). All the patients with ReA and ReTEB were negative for RF. The mean (SD) ESR and CRP values were 15 (14) mm/1st h and 5 (7) mg/l in the ReA subgroup and 9 (4) mm/1st h and 3 (2) mg/l in the ReTEB subgroup, respectively.

### Matched patient-control pairs

Because joint symptoms occur frequently in the community, we compared musculoskeletal symptoms in the *Shigella* positive patients and controls matched for age, sex and municipality (table 2). The mean age of 190 patient-control pairs was 38.0 years (range 2–73). Of these pairs, 3% were under 16 years of age, and 64% were female.

Joint or other musculoskeletal symptoms during the past 6 months were reported by 74/184 (40%) patients and by 51/184 (28%) control subjects (OR = 1.74, 95% CI 1.13 to 2.68, *p* = 0.021).

### Table 2 Comparison of musculoskeletal diagnoses of the 190 matched case-control pairs based on questionnaire or on clinical examination

<table>
<thead>
<tr>
<th>Musculoskeletal diagnoses</th>
<th>Patients</th>
<th>Control subjects</th>
<th>OR</th>
<th>95% CI</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute musculoskeletal symptoms</td>
<td>58</td>
<td>15</td>
<td>5.12</td>
<td>2.78–9.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>15</td>
<td>1</td>
<td>16.2</td>
<td>2.12 to 123.93</td>
<td>0.001</td>
</tr>
<tr>
<td>Reactive tenosynovitis, enthesisopathy, or bursitis</td>
<td>4</td>
<td>0</td>
<td>†</td>
<td>†</td>
<td>0.125</td>
</tr>
<tr>
<td>Postinfective arthritis or lumbar pain</td>
<td>23</td>
<td>0</td>
<td>†</td>
<td>†</td>
<td>0.001</td>
</tr>
<tr>
<td>Arthritis or lumbar pain during infection</td>
<td>9</td>
<td>3</td>
<td>3.10</td>
<td>0.83 to 11.63</td>
<td>0.146</td>
</tr>
<tr>
<td>Other acute musculoskeletal symptoms</td>
<td>7</td>
<td>11</td>
<td>0.62</td>
<td>0.24 to 1.64</td>
<td>0.332</td>
</tr>
<tr>
<td>Chronic/post musculoskeletal diseases</td>
<td>11</td>
<td>34</td>
<td>0.28</td>
<td>0.14 to 0.58</td>
<td>0.01</td>
</tr>
<tr>
<td>Degenerative musculoskeletal disease</td>
<td>6</td>
<td>10</td>
<td>0.59</td>
<td>0.21 to 1.65</td>
<td>0.549</td>
</tr>
<tr>
<td>Other chronic symptoms</td>
<td>5</td>
<td>24</td>
<td>0.19</td>
<td>0.07 to 0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Unclassified</td>
<td>5</td>
<td>2</td>
<td>2.54</td>
<td>0.49 to 13.26</td>
<td>0.453</td>
</tr>
</tbody>
</table>

Note: *Data presented as pairs from McNemar’s test; †non-calculable. OR, odds ratio; 95% CI, 95% confidence interval.*
A longer duration of enteritis had occurred in patients with ReA triggered by *Salmonella* and by *Campylobacter* than with uncomplicated patients, while the reverse occurred in *yersinia*. We found no statistically significant difference in the duration of diarrhoea in *Shigella* patients with reactive musculoskeletal complications compared with those with an uncomplicated course.

*Shigella* triggered ReA in children is uncommon. We observed no child with ReA. Therefore, in agreement with previous studies, ReA seems to be a rare complication of enteritis in children, as observed also in association with *Salmonella*, *Yersinia*, and *Campylobacter* infections.

In our patients with ReA, occurrence of the antigen HLA-B27 was 36%, a figure lower than reported in outbreak studies, where HLA-B27 has been positive in 86% (18/21) of patients tested. This figure, however, is higher than the frequency of HLA-B27 (14%) in the general Finnish population. In our study, interestingly, the positivity of antigen HLA-B27 was 67% with *S flexneri* and 30% with *S sonnei*, whereas in those above-mentioned epidemics the *Shigella* species involved was *S flexneri*. Our results thus may indicate that the presence of HLA-B27 has a more important role as a marker of ReA attributable to *S flexneri* than to *S sonnei*.

The following factors indicate the reliability of our data and the diagnostic accuracy of our study. Firstly, because our material was based on a nationwide recording of patients with a positive stool culture for *Shigella*, no selection bias occurred, and confirmation of the triggering infection was certain. Secondly, we based our diagnosis of ReA on a questionnaire we successfully used previously. Thirdly, our response rate was high. Fourthly, our results were based not on a questionnaire data but also patients with reactive musculoskeletal symptoms were studied clinically. Finally, because joint complaints are common in the community, we used controls matched for age and sex to validate diagnoses of patients with reactive symptoms.

In summary, ReA occurred in about 7% of patients with *Shigella* infection, with other reactive musculoskeletal symptoms (tendonitis, enthesopathy, bursitis) also observed. In addition to *S flexneri*, *S sonnei* and *S dysenteriae* should be included among the triggering agents of ReA.

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