

EXTENDED REPORT

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

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Objectives: 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 (tendonitis, enthesopathy, or bursitis). Of the 14 patients with ReA, all adults, 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 reported *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*,^{3 4} but *S sonnei* has been reported in a few cases.^{5 6} One case report also exists in which the triggering species was *S dysenteriae*.⁷

In medical reports published in English, the few rheumatological surveys on *Shigella* outbreaks show occurrences of ReA of between 1.5% and 4%,^{4 8–10} 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 (55%), 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.¹¹

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

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

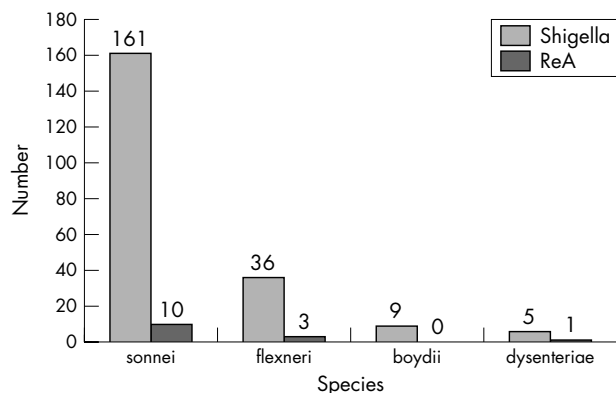


Figure 1 Occurrence of *Shigella* species and reactive arthritis among the 211 *Shigella* patients with a positive stool culture.

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.¹²

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.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.

Table 1 Clinical characteristics of patients with ReA and with ReTEB

Characteristics	ReA	ReTEB
No of patients	14	4
Age (years), mean (range)	43.9 (25–73)	42.7 (33–50)
Sex, male/female	5/9	1/3
Patients with peripheral arthritis, No (%)	10 (71)	0
Patients with inflammatory low back pain, No (%)	4 (29)	0
Onset of musculoskeletal symptoms (days from onset of diarrhoea), median (range)	3 (0–40)	33 (4–44)
Patients with other musculoskeletal symptoms, No (%)		
Low back pain	11 (79)	1 (25)
Neck pain	7 (50)	1 (25)
Heel pain	3 (21)	1 (25)
Bursitis	0 (0)	2 (50)*
Tendonitis	1 (7)†	1 (25)‡
Achilles tendon pain	1 (7)	0 (0)
Enthesopathy	1 (7)	0 (0)
Other	2 (14)§	1 (25)¶

*Bursitis of the knee in one and of the trochanter bursitis in the other; †tendonitis of the wrist; ‡tendonitis of the supraspinatus tendon; §pain in the thoracic spine in one, and pain and swelling of the palm of one hand in the other; ¶lateral epicondylitis.

Statistical analysis

Proportional data were compared with the χ^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 system 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 ($\geq 37.5^\circ\text{C}$). 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 sonnei* 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 tendonitis, 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

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

Musculoskeletal diagnoses	Patients	Control subjects	OR	95% CI	p Value
<i>Acute musculoskeletal symptoms</i>	58	15	5.12	2.78–9.44	<0.001
Reactive arthritis	15	1	16.2	2.12 to 123.93	0.001
Reactive tendonitis, enthesopathy, or bursitis	4	0	†	†	0.125
Postinfective arthralgia or lumbar pain	23	0	†	†	<0.001
Arthralgia or lumbar pain during infection	9	3	3.10	0.83 to 11.63	0.146
Other acute musculoskeletal symptoms	7	11	0.62	0.24 to 1.64	0.332
<i>Chronic/past musculoskeletal diseases</i>	11	34	0.28	0.14 to 0.58	0.01
Degenerative musculoskeletal disease	6	10	0.59	0.21 to 1.65	0.549
Other chronic symptoms	5	24	0.19	0.07 to 0.50	0.001
<i>Unclassified</i>	5	2	2.54	0.49 to 13.26	0.453
Total number of patients/controls with musculoskeletal symptoms	74	51	1.74	1.13 to 2.68	0.021

*Data presented as pairs from McNemar's test; †non-calculable. OR, odds ratio; 95% CI, 95% confidence interval.

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 (Egypt and India, three each; Turkey, two; Kenya, Congo, Thailand, the Philippines, Dominican Republic, and Spain, one each). Of these patients, 10 had positive stool culture for *S sonnei*, three for *S flexneri*, and one for *S dysenteriae* (fig 1). Occurrence of ReA did not differ statistically significantly between the *S sonnei* (6%), *S flexneri* (8%), *S dysenteriae* (20%), and *S boydii* (0%) groups ($p = 0.492$; χ^2 test).

Four of the patients with ReA had only inflammatory low back pain without peripheral arthritis (table 1). The other 10 patients had peripheral arthritis, which was monoarticular in two, oligoarticular (two to four affected joints) in three, and polyarticular in five. The most commonly affected joints were the wrists (60%), followed by the distal interphalangeal joints of the hands (40%), metatarsophalangeal joints, metacarpophalangeal joints, and the proximal interphalangeal joints of the hands (30% for each), knees and elbows (20% for each), and ankles (10%). The size of joints affected was large in one and small in six patients; three (30%) had both large and small joints affected. Both upper and lower extremities were affected in four patients (40%); only the upper extremities in five, and only the lower in one. Pre-existing inflammatory rheumatic disease was present in two men who had ankylosing spondylitis and one woman with seronegative rheumatoid arthritis.

The arthritis in most cases was mild. Eight of the 14 patients with ReA (57%) had visited a physician because of

arthritis, but only two had sufficiently severe arthritis to require admission to hospital. Duration of acute ReA could be determined for the half of patients who had fully recovered from the arthritis by the clinical examination: ≤ 1 month in four patients, 1–2 months in one patient, and 2–3 months in two. In the rest, continuing arthritis was still evident at the time of clinical examination; of these patients, the longest duration of acute ReA was 6 months.

Patients with *Shigella* triggered ReTEB

Among the four patients with ReTEB, 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* ($p = 0.331$; χ^2 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, $p = 0.021$).

ReA occurred mainly in the *Shigella* patient group (OR = 16.2, 95% CI 2.12 to 123.93, $p = 0.001$); only one control subject had ReA attributable to a urological infection. Chronic joint complaints or previous musculoskeletal disease (especially degenerative symptoms or chronic joint pain) were more common in the controls than in the *Shigella* group (table 2).

DISCUSSION

As far as we know, this is the first population based study on the prevalence of joint symptoms in patients with a positive stool culture for *Shigella*. Based on calculations at the clinical examination, occurrence of *Shigella* triggered ReA was 6.6%. This figure is somewhat higher than in outbreak studies with reported occurrences of between 1.5% and 4%.^{4–8–10} When we included the other reactive musculoskeletal symptoms (tendonitis, enthesopathy, or bursitis) the total rose to 8.5%. When questionnaire data with no clinical examination were included the occurrence of ReA rose to 7.1%, and with other musculoskeletal symptoms, to 9.5%. In Finland, with about 100 identified *Shigella* infections annually (National Infectious Disease Registry), the actual minimum incidence of reactive musculoskeletal symptoms after shigellosis is 1.6/1 000 000 population per year and of ReA 1.3/1 000 000. Moreover, we estimated the risk for developing ReA in association with *Shigella* infection; this risk was high (OR = 16.2). Although the corresponding 95% CI interval was broad, indicating that the study series was epidemiologically small, this association was statistically highly significant.

On the basis of outbreak studies, it has been suggested that, unlike *S flexneri*, *S sonnei* is not arthritogenic.^{4–13} This finding has been attributed to a sampling error.¹⁴ Another reason might be that the particular strains causing those epidemics were not arthritogenic. On the other hand, *S sonnei* associated ReA has been documented in some case reports,^{5–6} and one case report also of ReA in association with *S dysenteriae* infection.⁷ In the present series, the incidence of ReA attributable to *S sonnei* (6%) and to *S flexneri* (8%) was of the same magnitude. Moreover, one of the five patients with *S dysenteriae* infection developed ReA. Because we could not obtain the results of stool specimens for other ReA associated microbes (*Salmonella*, *Campylobacter*, and/or *Yersinia*) in our patients, it can be reasoned that we cannot with certainty exclude the possibility that ReA was co-triggered by some of those microbes. However, none of the *Shigella* patients reported in the questionnaire or at the clinical examination any concurrent intestinal infections. Our findings thus confirm the evidence of previous case reports that *S sonnei* and *S dysenteriae* are triggering agents in ReA.

In addition to ReA, four patients had reactive tendonitis or enthesopathy or bursitis (ReTEB). The concept of reactive enthesitis was first used by Thomson *et al* in association with *Salmonella* triggered ReA.¹⁵ Reactive enthesitis and ReTEB are analogous concepts of ReA and describe patients with these musculoskeletal manifestations but without synovitis of the peripheral joints. Tendonitis or enthesopathy have been previously reported in association with *Shigella* induced ReA,^{6–8–16} but, to our knowledge, not bursitis. In the present series, the prevalence of ReTEB was about 2%, a result much in line with our previous population based finding for *Campylobacter* triggered ReA.¹²

The clinical picture of *Shigella* triggered ReA was, in half our cases, polyarticular, with arthritis found often in the small joints of the hands or the feet. This clinical manifestation of ReA has previously been reported in ReA attributable to *Shigella*^{4–10} and was also noticed in our earlier community based study of *Campylobacter*.¹²

A longer duration of enteritis had occurred in patients with ReA triggered by *Salmonella*¹⁷ and by *Campylobacter*¹² than with uncomplicated patients, while the reverse occurred in yersiniosis.¹⁸ 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.^{3–16–19} 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*,²⁰ *Yersinia*,²¹ and *Campylobacter*¹² 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.^{4–9–10–22} This figure, however, is higher than the frequency of HLA-B27 (14%) in the general Finnish population.²³ 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.¹² Thirdly, our response rate was high. Fourthly, our results were based not only on 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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