Reactive Joint Symptoms Following an Outbreak of *Salmonella typhimurium* Phage Type 135a

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ABSTRACT. ***Objective.*** To quantify the incidence and clinical features of reactive arthritis (ReA) developing in a cohort exposed to an outbreak of *Salmonella typhimurium* phage type 135a, and factors affecting host susceptibility to ReA.

Methods. A screening questionnaire was mailed to 493 patients with confirmed *Salmonella* infection. Musculoskeletal symptoms and extraarticular manifestations of ReA were quantified. Positive responders with joint pain were invited to participate further, with a detailed history, examination, and investigations including HLA-B27 status.

Results. A total of 261/461 (57%) subjects responded to the questionnaire, with 23/54 adults (43%) and 41/207 children (20%) reporting joint symptoms. Although joint pains were less common in children compared with adults, those children affected usually had eye (34%) or mucocutaneous (37%) symptoms. The incidence of ReA was 14.6%, with adults more frequently affected (24%) than children (12%). This may be an underestimate given the large proportion of children involved. Associated clinical features were similar to previous studies, with the distribution of arthritis affecting the lower limbs predominantly in an oligoarticular pattern, as were the extraarticular manifestations and enthesopathy. We found 17% of subjects were HLA-B27 positive, and 55% were still symptomatic after 6 months.

Conclusion. In an Australian cohort study of a *S. typhimurium* phage type 135a outbreak, joint symptoms were common, affecting 25% of subjects. The incidence of ReA of 14.6% and the clinical features were comparable to previous studies. There was a small effect of HLA-B27 status on the development of ReA. (J Rheumatol 2005;32:524–7)

Key Indexing Terms:
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Reactive arthritis (ReA) is an inflammatory asymmetric peripheral oligoarthritis, associated in some patients with sacroiliitis and enthesopathy, that develops after infection of the gastrointestinal or genitourinary tracts[1]. The weight-bearing lower limb joints are most often affected after a delay of up to a few months, and may be associated with mucocutaneous and systemic features[2]. ReA develops in a subgroup of individuals exposed to Yersinia, Shigella, Salmonella, Campylobacter, and Chlamydia species, with HLA-B27 positive subjects being at greater risk, and having potentially more severe and prolonged symptoms[3].

In February 1999, an outbreak of *Salmonella typhimurium* phage type 135a food poisoning occurred in South Australia. Phage type 135a has not been previously studied and this was an opportunity to characterize the features related specifically to infection with this phage type. We quantified the incidence and clinical features of ReA that developed and investigated factors affecting host susceptibility to ReA.

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MATERIALS AND METHODS

The Communicable Diseases Section of the Department of Human Services identified subjects who had by law been reported to them; subjects had S. *typhimurium* phage type 135a infection from contaminated orange juice, based on positive fecal culture reports received between February and June 1999. A screening questionnaire was mailed to 493 subjects 6 to 12 months later to establish their demographic details, musculoskeletal symptoms, and any extraarticular manifestations (e.g., mouth ulcers, rash, conjunctivitis, recurrent diarrhea).

Positive responders with joint pain were invited to participate further after signing a consent form, with a more detailed history, clinical examination, and investigations 18 to 24 months after the positive stool cultures. Radiographic assessment of persistently involved joints was performed and HLA-B27 status determined. Subjects under 16 years of age were offered the option of a buccal swab to obtain DNA for HLA-B27 polymerase chain reaction (PCR) analysis, instead of a blood test for flow cytometry.

ReA was defined as the development of pain in a previously healthy joint within the first 3 months of the onset of diarrhea[2], with or without extraarticular features typical of ReA. History or examination findings consistent with inflammatory arthritis were desired, including a history of parental observation of joint swelling in children. Statistical analysis was performed using the chi-squared method, with p values less than 0.05 considered significant. Fisher's exact test was used where appropriate. The local hospital ethics committee approved the study.

RESULTS

Four hundred ninety-three questionnaires were posted, with 32 returned as no longer at their contact address. In total, 261/461 subjects responded to the questionnaire (57% response rate), with mean age 15 years ± 12.6 SD (range 1–66 years). Of those who gave details on sex, there were similar numbers of males and females (92 males, 86 females, ratio 1.07:1). The frequency of reported symptoms in adults and children, with and without joint pain, is described in Table 1. Joint symptoms, including pain, stiffness, or swelling, were reported on the screening questionnaire in 25% of subjects, being significantly less common in children (41/207, 20%) compared with adults (23/54, 43%) (chi-square = 12.0, p = 0.001). Of those with joint pain, a further detailed history was obtained from 17 adults and 29 children, with 13 adults and 25 children having further joint examination and investigations. Six adults and 12 children were not contactable by telephone or letter and therefore could not be fully assessed.

In the adult population, there was no significant relationship between skin, eye, or diarrheal symptoms and the presence or absence of joint pain. Overall, recurrent diarrhea (loose bowel motions lasting 2–3 days, recurring 2–4 weekly) was more common in adults compared to children (33% vs 15%; chi-square = 9.5, p = 0.002). There was a trend towards recurrent diarrhea in those adults with joint symptoms compared with those without joint pain (chi-square = 1.9, p = 0.17). In subjects reporting joint pain, other extraarticular manifestations were less common in adults compared to children, with red eyes in 13% vs 34% (chi-square = 3.4, p = 0.07) and rash or mouth ulcers in 26% vs 37% (chi-square = 0.7, p = 0.39).

Children with joint pain often had associated extraarticular features, such as red eyes in 14/41 children (34%) and mucocutaneous symptoms in 15/41 (37%). A significantly greater number of children reported eye or skin symptoms in association with joint pain compared to those without joint pain (chi-square = 32.3, p < 0.001; chi-square = 11.3, p = 0.001, respectively). Recurrent diarrhea was also significantly associated with joint pain (chi-square = 5.6, p = 0.02), with 27% of children with joint pain having ongoing diarrhea post-Salmonella gastroenteritis.

Knees were by far the commonest joint involved, with 61% of adults and 76% of children with knee pain or swelling. Ankles (25%), back (lumbar spine and sacroiliac joint pain, 20%), and wrists (17%) followed. The remainder of the joints were involved or symptomatic in less than 10% of subjects with joint pain identified. Enthesopathy, such as Achilles tendonitis or plantar fasciitis, was seen in 22% of subjects.

In our population, 13/54 adults (24%) and 25/207 children (12%) were diagnosed as having ReA after the above diagnostic criteria were applied, with a significantly greater proportion of adults affected (chi-square = 5.0, p = 0.03). The overall rate of ReA was 14.6% in the 261 responders.

Within the ReA group, associated recurrent diarrhea was common (34%), with mucocutaneous symptoms (29%) and red eyes (24%) in a smaller proportion. There was no significant difference between the occurrence of red eyes or mucocutaneous symptoms in adults versus children. However, a trend towards more recurrent diarrhea in adults (54%) compared with children (24%) was seen (chi-square = 3.4, p = 0.07). Joint involvement was monoarticular in 8%, oligoarticular (2 to 4 joints) in 61%, and polyarticular (5 or more joints) in 31%.

With regard to other risk factors for the development of ReA, we were unable to obtain accurate information on the exact duration of the initial diarrheal episode, with great variability in the subjects' abilities to recall this information. The use of antibiotics during the acute diarrheal phase was uncommon (2/29 children and 3/17 adults). Of those diagnosed with ReA who have had further testing to determine their HLA-B27 status, only 4/20 (20%) children and 1/10 (10%) adults were positive. In those with persistent symptoms or objective signs of continuing joint involvement who had radiographs performed, 4 adults and no children had abnormalities detected. These included changes suggestive of enthesitis as well as degenerative disease in the lumbar spine, sacroiliac joints, hands, and shoulders.

Table 1. Frequency of symptoms in adults and children, with and without joint pain, by self-report questionnaire.

	Joint Pain (%)	Mucocutaneous Symptoms (%)	Recurrent Diarrhea (%)	Eye Symptoms (%)
Adults				
Joint pain	23/54 (43)*	6/23 (26)	10/23 (44)	3/23 (13)
No joint pain	—	6/31 (19)	8/31 (26)	5/31 (16)
Total	23/54 (43)	12/54 (22)	18/54 (33)	8/54 (15)
Children				
Joint pain	41/207 (20)	15/41 (37)**	11/41 (27)†	14/41 (34)††
No joint pain	—	23/166 (14)	20/166 (12)	7/166 (4)
Total	41/207 (20)	38/207 (18)	31/207 (15)	21/207 (10)

* Adults compared with children, chi-square = 12.0, p = 0.001. ** Compared to without joint pain, chi-square = 11.3, p = 0.001 † Compared to without joint pain, chi-square = 5.6, p = 0.02. †† Compared to without joint pain, chi-square = 32.3, p < 0.001.

The course of ReA was recurring or persistent in the majority of those studied, with symptoms present longer than 6 months in 55%. The joint complaints resolved within a month in 26% and were limited to less than 6 months in 18%. In adults, 5/13 were fully resolved at our review between 17 and 24 months after the initial diarrheal event, and 13/25 children were asymptomatic, a nonsignificant difference.

DISCUSSION

This is one of the largest epidemiological studies analyzing the incidence of reactive joint complications after Salmonella gastroenteritis. In a point-source community outbreak affecting 493 people, our questionnaire response rate of 57% was significantly higher than in other similar studies[4,5]. Another Australian study involving 2 outbreaks of *S. typhimurium* documented higher rates at 43% and 94%[6].

The time period post-exposure used in ReA classification criteria greatly influences the incidence estimates. Our overall rate of 14.6% is reduced to 9.6% if we use a 4 week cutoff period for the diagnosis of ReA rather than 3 months. Of the subjects exposed to *S. typhimurium* in a Finnish study, 8% were diagnosed with ReA when a definition requiring synovitis within a few weeks of gastroenteritis was applied[7]. In a proposal for classification of patients entering clinical and experimental studies on ReA, Pacheco-Tena, *et al* suggested that 6 weeks should be the maximal time period between an infectious trigger and the onset of musculoskeletal symptoms[8]. However, the timeframes varied between 4 weeks and 3 months, with the latter chosen for our study based on the diagnostic criteria validated for use in a population setting by Thomson, *et al*[2].

Joint pain was reported on the screening questionnaire in 25% of our subjects, comparable with previous reports of subjective joint involvement that ranged from 12% to 40%[6,7,9-12]. Joint symptoms were significantly less common in children compared with adults.

The reported incidence of ReA after Salmonella exposure varies from 1.6%[13] to 15%[14,15], and is comparable to our overall rate of 14.6%. If nonresponders were less likely to have developed ReA by virtue of failure to respond to the survey (selection bias), then our estimate of 14.6% ReA probably represents a maximum frequency estimate. Conversely, this may be an underestimate, as our group consisted of a large proportion of children, who are less likely to develop the extra-enteric symptoms[10,16].

Studies with at least half the subjects under 16 years of age reported Salmonella ReA rates of between 0.2% and 3%[14,17]. A Finnish study comprising 63% of subjects less than 16 years of age reported joint symptoms in 18%, with an overall ReA rate of 6.9%[14]. Only 3% of children exposed developed ReA. A higher rate of ReA in children of 8% was reported in an outbreak of S. *bovismorbificans*[11], with another small outbreak of *S. typhimurium* phage type 193 resulting in no children developing ReA[7]. Our study involved a large number of children, with 79% under 16 years old at the time of Salmonella infection. The age distribution of subjects with positive fecal cultures is shown in Table 2. Children may be generally less susceptible to ReA, due to either a more naive immune system or alternatively, greater efficiency of bacterial elimination[18].

A significantly greater proportion of our adults (24%) compared with children (12%) developed ReA. This may be an overestimate when compared to previous studies that used stricter criteria, such as requiring the presence of extraarticular manifestations or objective signs of synovitis. The arthritogenic potential, however, even among *S. typhimurium*, may vary[19]. Infection with *S. typhimurium* phage type 193 resulted in only 8% ReA and there was no effect of HLA-B27 status on the duration or severity of joint complaints[7].

In those children reporting joint pain, extraarticular manifestations were usually present. This is in contrast to studies showing that extra-enteric symptoms after *Salmonella* gastroenteritis are rare among young subjects[10,16]. A recent *S. enteritidis* outbreak affecting 286 children resulted in only mild arthralgias involving the lower limbs in 2%, with no extraarticular features reported[18]. Adults with joint pain in our study less commonly had associated extraarticular features, consistent with previous studies[3,4,20,21].

The knee joint was most commonly involved, followed by ankles, lumbar spine or sacroiliac joints, and wrists. This is in keeping with previous studies with lower limb predominance. ReA is typically oligoarticular in expression, as recorded in 61% of our subjects, although 46% of adults in our study had polyarticular involvement.

In the subgroup that had HLA-B27 status determined, 10% of adults and 20% of children were HLA-B27 positive, with an overall rate of 16.7%. This is roughly double the rate in the general Australian population of between 7% and

Table 2. Distribution of age groups with positive fecal cultures.

Age Range, yrs	Percentage
0–4	29
5–9	20
10–14	16
15–19	11
20–24	9
25–29	7
30–34	1
35–39	2
40–44	3
45–49	1
50–54	0
55–59	0
60–64	0
65–69	0
70–74	0
75–79	1

9%[20], producing an estimated relative risk of 2.3. Previous studies have reported much higher rates, from 19% to 100%[3,21], and therefore a closer association between HLA-B27 positivity and development of ReA, or its severity and chronicity.

The link between HLA-B27 positivity and ReA development is now less clear and may reflect disease severity rather than susceptibility, with the frequency of HLA-B27 positive subjects much lower in community-based compared with hospital-based series[1]. In an Australian study, McColl and colleagues[6] suggested that their low prevalence of HLA-B27 positivity of 10.5% in ReA cases reflected a cohort who were yet to be selected for severe or prolonged disease, as compared with studies from tertiary referral centers. The frequency is reported to be up to 50% only in enteric and urogenital ReA[22]. The lower frequency of HLA-B27 in our patients with Salmonella ReA may reflect the development of milder forms of the disease.

The prognosis is usually favorable in Salmonella ReA[23], with most patients recovering within 3 to 5 months[24]. The majority of our subjects had a persistent or recurrent course, with 55% being symptomatic for longer than 6 months, a higher proportion than in previous studies of 7% to 31%[14,15]. Disease activity at 6 months is thought to be the most important risk factor clinically for ongoing ReA symptoms[5], and a 6 month cutoff point for differentiating between acute and chronic ReA has been recommended[25].

In our Australian cohort study of a *Salmonella typhimurium* phage type 135a outbreak, joint symptoms were common, affecting 25% of subjects, with an incidence of ReA of 14.6%. This may be an underestimate, given the large proportion of children, who are less likely to develop ReA. There was a small effect of HLA-B27 status on the development of ReA. Prompt prospective recruitment and study of subjects affected by point-source outbreaks of ReA associated pathogens will further delineate the pathological basis of the arthropathy and arthritis that commonly results.

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