

Reactive Arthritis and Other Sequelae Following Sporadic *Salmonella typhimurium* Infection in British Columbia, Canada: A Case Control Study

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ABSTRACT. Objective. To describe sequelae occurring in the 3 months after sporadic *Salmonella typhimurium* (ST) infection in British Columbia (BC), Canada.

Methods. We compared the incidence of sequelae to similar symptoms in controls; identified risk factors for developing sequelae; identified the incidence of reactive arthritis (ReA) as diagnosed by a rheumatologist, and assessed primary care physician diagnosis of ReA. A questionnaire was administered by telephone to cases of ST occurring in BC between December 1, 1999, and November 30, 2000; and to controls obtained from the BC provincial client registry. Cases reporting symptoms were followed up by a rheumatologist.

Results. Thirty-five of 66 (53%) cases reported any symptom, 17 (26%) reported joint symptoms. The Mantel-Haenszel odds ratio (weighted by sex and pediatric/adult) of a salmonella case reporting "any symptom" compared to controls was 5.42; 95% confidence interval (CI) 2.18–16.27; and reporting joint symptoms was 4.40; 95% CI: 1.25–19.53. The sex distribution of cases reporting joint symptoms was not significantly different. No medication taken during the salmonella infection was significantly different between the cases who had joint symptoms and those who did not. Four cases (2 adults, 2 children) were considered by the rheumatologist to have symptoms consistent with ReA, 2 of these had been told by a physician that their symptoms were related to their ST infection.

Conclusion. Cases were more than 4 times more likely to report joint symptoms than controls; and despite the loss of many cases to followup, 6% of all cases were considered to have ReA. (J Rheumatol 2002;29:2154–8)

Key Indexing Terms:

REACTIVE ARTHRITIS

SALMONELLA TYPHIMURIUM

SEQUELAE
CASE CONTROL

Reactive arthritis (ReA) is an acute sterile inflammation of the joints that complicates infection elsewhere in the body. It usually occurs 1–2 weeks after nongonococcal (*Chlamydia trachomatis*) urethritis or infectious dysentery caused by *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia*. "Reiter's syndrome" describes the classic triad of arthritis accompanied by conjunctivitis and urethritis. Inflammation may occur at other sites causing mucocutaneous lesions of the oropharynx, penis, and soles of the feet, and erythema nodosum. The pattern of joint involvement in Reiter's

resembles ReA, although a causal bacterial trigger may not be demonstrated.

ReA has been reported to occur in 6–15% of cases of salmonella dysentery^{1–6}. Much of the knowledge about post-salmonella infection ReA is from individuals who have been exposed to the same microorganism by a point source^{1–5}. Studies have shown that the genetic type HLA-B27 is a predisposing factor in over two-thirds of patients with ReA; those who are negative for HLA-B27 may be positive for cross reactive group antigens HLA-B7, B22, B40, and B42.8^{7,2}. Others have shown an association between ReA and the duration of the gastrointestinal illness⁸.

We performed a multiprovincial *Salmonella typhimurium* (ST) case-control study in 4 Canadian provinces to identify risk factors, burden of illness, and geographic distribution of ST definitive type (DT)104 and non-DT104.

MATERIALS AND METHODS

Between December 1, 1999, and November 30, 2000, a detailed questionnaire was administered to all ST cases (persons who experienced diarrhea and had a stool culture from which ST was isolated) in British Columbia (BC), Alberta, Saskatchewan, and half of the cases in Ontario. Age-matched controls were randomly obtained from the provincial registered persons database of each participating province. These databases have

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information, including date of birth and address, on all persons living in the province eligible for provincial health coverage. The BC cases and controls were further followed up to identify possible sequelae symptoms; this information was combined with BC risk factor and illness details from the multiprovincial study.

Description of sequelae. We described sequelae occurring in the 3 months following sporadic typhimurium infection in BC by:

(1) Comparing the incidence of symptoms in cases (as identified by a questionnaire administered post-salmonella infection) to similar symptoms in controls; (2) identifying risk factors for developing sequelae (as identified by a questionnaire); (3) identifying the incidence of ReA as diagnosed by a rheumatologist; and (4) assessing primary care physician diagnosis of ReA.

Subjects. Cases. All cases of ST identified on stool culture between December 1, 1999, and November 30, 2000, by the BC provincial laboratory, who participated in the multiprovincial ST risk factor study, and who on previous questioning had consented to being re-contacted.

Controls. All BC controls who participated in the multiprovincial ST risk factor study and who on previous questioning had consented to being re-contacted.

The questionnaire was developed following a literature review including the QUEST 2 (Questionnaire Utilizing Epidemic Spondyloarthropathy Traits), a validated questionnaire used to screen populations with gastroenteritis for symptoms of ReA⁹, and discussion with experts. It was piloted on cases and controls identified in the multiprovincial pilot study that took place in BC during the month of November 1999.

The questionnaire included items to identify the following:

- Peripheral arthritis: joint pain, joint swelling, joint redness or warmth, joint stiffness
- Lower back and buttock pain
- Periarticular symptoms: heel pain
- Mucocutaneous symptoms: mouth sores/ulcers, genital sores, rash; red, painful, burning, or itching eyes
- Neurologic symptoms: dizzy spells, double vision, paresthesia, weakness of hands/legs
- Urethritis (males only): dysuria, penile discharge
- Constitutional symptoms: fever, weight loss
- Taking antibiotics after the onset of diarrhea for any reason
- If symptomatic, whether a physician told them that the current problem was related to ST infection.

Two new aggregate variables were created: joint symptoms (one or more of peripheral arthritis symptoms, lower back and buttock pain) and any symptom (one or more of any of the symptoms).

Ethical approval for the sequelae study was obtained from the University of British Columbia Behavioural Research Ethics Board.

A trained interviewer from the BC Centre for Disease Control contacted the cases and controls 3–4 months after the onset of diarrhea. Verbal consent was obtained and a brief questionnaire was administered to screen for sequelae occurring within 3 months of the initial salmonella infection (for cases) and symptoms occurring over the same 3 month period for controls. A rheumatologist then contacted all case-persons who identified possible sequelae symptoms and who consented to a further telephone interview. ReA was diagnosed by the rheumatologist when the cases (or parent/guardian for pediatric cases) described peripheral synovitis as defined by the European Spondylarthropathy Study Group¹⁰.

To increase the power of the study, all cases and all controls willing to participate were interviewed, even if no matched cases or controls were available. Questionnaire responses were entered into Epi Info (Version 6). The sequelae study data file was merged with the completed BC component of the multiprovincial ST case-control study containing demographic, risk factor, and burden of illness information.

Analysis. Analyses were performed for the following subgroups: pediatric (less than 12 years of age at the time of the initial multiprovincial interview, i.e., a parent or guardian responded to the questionnaire), adult (12 years and over), and all (pediatric and adult).

Measures of statistical association were determined using Mantel-Haenszel chi-square and Fisher's exact test (where an expected value was less than 5) for comparison of proportions. In the case-control analysis, unmatched odds ratios were calculated by comparing the frequency of symptom occurrence in all cases versus all controls using exact 95% confidence limits for the maximum likelihood estimate.

In the case-case analysis, the frequency of sequelae was compared for the following subgroups of cases: cases who took medication after infection versus those who did not, and cases dichotomized at mid-time of diarrhea duration (Figure 1), i.e., ≤ 14 days versus > 14 days.

P values were not adjusted for multiple comparisons.

RESULTS

Sixty-six cases (31 male, 35 female) and 48 controls (29 male, 19 female) were included in the BC sequelae dataset (Table 1). The age distribution of cases and controls was not significantly different (Table 2). Sex, questionnaire answered, and reported symptoms data are shown in Table 3.

Case-control symptom analysis. There was no significant difference between cases and controls reporting joint pain, swollen joints, redness over the joint or pain in the buttock. Reports of stiff joints, lower back pain, and joint symptoms were significantly different between cases and controls (Table 4).

The Mantel-Haenszel (weighted by sex and pediatric/adult) odds ratios (OR) of a case of salmonella reporting "any symptom" compared to controls was 5.42 [95% confidence interval (CI): 2.18–16.27 ($p = 0.0002$)], and reporting "joint symptoms" was 4.40 (95% CI: 1.25–19.53).

The sex distribution of cases reporting joint symptoms was not significantly different (8 of 35 females and 9 of 31 males): OR = 0.72 (95% CI: 0.21–2.53). The incidence of other symptoms is shown in Table 5.

Case-case analysis. None of the drugs taken during the salmonella infection (antibiotics, anti-diarrheal medication, medication for nausea and vomiting, or other medication) were significantly different between the cases who had joint symptoms and those who did not. However, antibiotics were taken by 4 of 17 cases with joint symptoms and 24 of 47 cases without joint symptoms (OR 0.29; 95% CI: 0.07–1.18).

Measures of statistical association were examined for dichotomized diarrhea duration and all variables, for adult, pediatric, and combined groups. Table 6 shows the significant symptoms.

Rheumatologic followup. Thirty-five of the 66 cases included in this study reported any symptom. Eight (4 adult, 4 pediatric) of these declined followup by a rheumatologist — only one of these had joint symptoms. Four adult cases (all males with joint symptoms) and 2 pediatric cases (1 male, 1 female, neither with joint symptoms) were lost to

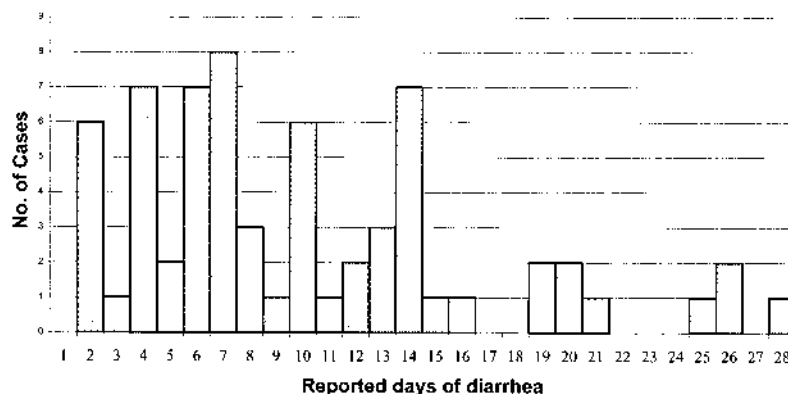


Figure 1. Duration of diarrhea reported by cases. Mean duration of diarrhea 12 days, median 8.5 days.

Table 1. Cases and controls in the sequelae study.

	Total Multiprovincial Study (BC Dataset)	
	Cases	Controls
	87	59
Reasons for exclusion		
Isolate not enteric (foot swab)	1	—
Requested not be contacted again	3	0
Contacted but refused to participate in sequelae study	6	6
Phone not in service/wrong #/person moved	9	3
Not reached	3	2
Total excluded	21	11
Total in BC sequelae study (% of total)	66 (76)	48 (81)

Table 2. Age distribution of cases and controls in sequelae study.

Age, yrs	Cases, % (n = 66)	Controls, % (n = 48)
< 10	47	41.7
10–19	9.1	8.3
20–29	7.6	8.3
30–39	15.2	18.8
40–59	10.6	10.5
60 and over	10.5	12.6
Total	100	100

Age distribution of cases and controls not significantly different, $p = 0.99$.

Table 3. Distribution of participants by sex, questionnaire answered, and reported symptoms.

	Pediatric Questionnaire		Adult Questionnaire		Total
	Male	Female	Male	Female	
Case	16	17	15	18	66
Any positive symptom (%)	7 (44)	8 (47)	9 (60)	11 (61)	35 (53)
Joint symptom (%)	2 (13)	3 (18)	7 (47)	5 (28)	17 (26)
Control	12	9	17	10	48
Any positive symptom (%)	2 (17)	3 (33)	2 (12)	1 (10)	8 (17)
Joint symptoms (%)	1 (8)	1 (11)	2 (12)	0 (0)	4 (8)

followup. Thus, 5 of 17 cases who reported joint symptoms were not contacted by the rheumatologist. Four of the 12 cases interviewed (all female; aged 7, 8, 31 and 35 yrs) were considered by the rheumatologist to have symptoms consistent with ReA. Three of the 4 cases assessed as ReA had duration of diarrhea greater than the mean (5, 16, 19, and 20 days). No cases were taking antibiotics prior to the salmonella infection and 2 had taken antibiotics after the symptoms of enteric infection occurred. The ethnicities reported by these 4 cases were: white (2), Canadian Chinese (1), and black (1).

Two of 4 subjects diagnosed with ReA had been told by physicians that their symptoms were related to their enteric infection; 2 had not been seen by a physician prior to the followup interview.

DISCUSSION

Much of what is known about post-salmonella ReA is derived from infectious outbreaks. We utilized the unique opportunity to combine risk factor and burden of illness information due to sporadic ST in BC over a 12 month period with sequelae symptoms, thus determining population-based frequency of sequelae. The study includes a control group for baseline prevalence of arthritis and other symptoms in a similar population in a 3 month period. About 8% of the controls reported joint symptoms, compared to 26% of the cases.

The report of symptoms outside the gastrointestinal tract

Table 4. Proportion of cases and controls with stiff joints/low back pain and “joint symptoms”.

	Cases with Symptoms	Controls with Symptoms	OR	95% CI	p*
Stiff joints					
All	9/62	0/46	∞	1.59–∞	0.01
Adult	7/30	0/26	∞	1.42–∞	0.012
Pediatric	2/32	0/20	∞	0.12–∞	0.517
Lower back pain					
All	9/59	0/48	∞	1.76–∞	0.004
Adult	6/29	0/27	∞	1.21–∞	0.024
Pediatric	3/30	0/21	∞	0.29–∞	0.259
Joint symptoms					
All	17/66	4/48	3.78	1.12–16.60	0.018
Adult	11/32	2/27	6.36	1.19–65.38	0.014
Pediatric	6/34	2/21	2.01	0.31–22.44	0.696

*p: Mantel-Haenszel chi-square and Fisher’s exact test 2-tailed (where an expected value was less than 5).

∞: Undefined as no controls with symptoms.

Table 5. Incidence of other sequelae symptoms.

	Cases		Controls		OR [95% CI]
	With	Without	With	Without	
Reported symptoms					
Heel pain, all subjects (%)	3 (5)	56	2	46	1.23 [0.13–15.31]
Sores in mouth, all (%)	8 (12.5)	56	1	46	6.49 [0.82–298]
Genital rash all (%), p = 0.037	6 (9.5)	57	0	47	∞ [0.91–∞]
Red eyes, all (%)	6 (9.5)	57	1	47	4.89 [0.56–232]
Red eyes, adult (%)	5 (16.7)	25	0	27	∞ [0.88–∞]
Painful eyes, all (%), p = 0.03	11 (18)	50	2	45	4.89 [0.99–47.74]
Painful eyes, adult (%), p = 0.004	8 (28.6)	20	0	26	∞ [1.90–∞]
Pain passing water, all male subjects (%)	5 (16.7)	25	0	28	∞ [0.92–∞]

p: Mantel-Haenszel chi-square and Fisher’s exact test 2-tailed (where an expected value was less than 5; only p < 0.05 shown).

∞: undefined as no controls with symptoms.

Table 6. Case analysis of duration of diarrhea (dichotomized 15 days: ≥ 15 days).

	OR	95% CI	p*
Stiff Joints			
All	0.08	0.01–0.65	0.007
Adult	0.06	0.00–1.10	0.03
Pediatric	0.08	0.00–9.04	0.19
Dizzy Spells			
All	0.1	0.01–0.77	0.012
Adult	0.07	0.00–1.10	0.03
Pediatric	0.18	0.01–14.7	0.29
Weak Legs			
All	0.09	0.01–0.64	0.007
Adult	0.05	0.00–0.83	0.016
Pediatric	0.13	0.00–12.06	0.25
Weight Loss			
All	0.19	0.02–1.30	0.049
Adult	0.12	0.00–1.77	0.08
Pediatric	0.35	0.01–24.53	0.42

* Fischer’s exact, 2 tailed.

by 53% (35/66) of the interviewees in this study is remarkably similar to the proportion reporting similar symptoms from a ST point source outbreak, 53% (170/321)⁴.

Limitations of our study include its retrospective design, reliance on subjective recollection of symptoms, and loss to followup of nearly 25% of cases from the multiprovincial data set. Also, 14 of 35 (40%) participants reporting any symptom in the sequelae study could not be followed up by a rheumatologist; however, this gives a conservative estimate of ReA.

Study participants were limited to those persons who could understand and speak English, so results may not be generalizable to other ethnic groups.

Questions regarding urethritis and penile discharge were included because they can present in post-dysenteric ReA, although not as frequently as with chlamydia infection. In one study urethritis occurred in 27% of patients with a confirmed diagnosis of reactive salmonella arthritis¹¹. In our study, we found 17% of males reported pain passing water

postenteric infection, compared with 0% in controls. However, this is a small sample and was not significantly different.

It has previously been found that although antibiotic treatment of the chlamydia infection may shorten the course or abort onset of ReA, use of antibiotics for ReA following enteric infections has not been effective⁶. Our study found that taking antibiotics may be somewhat protective, but this finding was not statistically significant.

ReA following urethritis is more common in males (ratio 20:1), yet previous studies have shown postenteric ReA affects men and women equally¹². Although all 4 cases of ReA diagnosed by a rheumatologist in our study were female, we cannot draw conclusions about sex ratio, as joint symptoms were reported by similar proportions (29% of males and 23% of females interviewed), and the 5 people with joint symptoms lost to followup were all male.

In some studies the incidence of ReA in children has been found to be less than in adults⁵; not a single case of arthritis was reported over a 4 month followup of salmonella infection in a large cohort of children in Germany¹³. In another study of single source salmonella there was no difference in the incidence of ReA between adults and children³. In our study of sporadic ST, children and adults were equally diagnosed with ReA.

The questionnaire was intended to be sensitive to identify all possible symptoms attributable to ReA and Reiter's syndrome. Thirty-five of 66 cases reported at least one symptom; unfortunately, 8 declined to be followed up by the rheumatologist and 6 more were lost to followup. Despite this, 4 of the 66 cases interviewed (6%) were diagnosed with ReA, which is compatible with previous reports^{1,2,4,5}.

A previous study found that none of 39 patients diagnosed with postenteric ReA had been diagnosed by their primary care physician as having arthritis related to their previous dysenteric illness and concluded that this could lead to incorrect diagnoses and therapy¹⁴. In our study, 2 of 4 subjects diagnosed with ReA had been told by physicians that their symptoms were related to their enteric infection and the other 2 had not been seen by a physician, since the onset of joint symptoms, prior to the followup interview.

In conclusion, cases were greater than 4 times more likely than controls to report joint symptoms, and despite the loss of many cases to followup, 6% of all cases were confirmed by a rheumatologist to have ReA.

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