

Incidence of Guillain-Barré Syndrome following Infection with *Campylobacter jejuni*

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Evidence of recent or ongoing *Campylobacter jejuni* infection has been found in approximately one out of every four cases of Guillain-Barré syndrome (GBS). It is increasingly accepted that *C. jejuni* infection is an important causal factor for GBS. However, the likelihood of GBS occurring following an episode of *C. jejuni* gastroenteritis has not been measured. The authors measured the incidence of GBS in a large cohort of persons with laboratory-confirmed *C. jejuni* infection. Cases of *C. jejuni* infection were derived from the Swedish national laboratory reporting system for the years 1987–1995. Follow-up for GBS was carried out using the Swedish national hospital inpatient register. Nine cases of GBS were detected in the cohort, which comprised 29,563 cases of *C. jejuni* infection—a rate of 30.4 per 100,000 (95% confidence interval: 13.9, 57.8). This compares with an expected incidence of 0.3 per 100,000 in a 2-month period in the general population. GBS is an important but rare complication of *C. jejuni* infection. The risk of developing GBS during the 2 months following a symptomatic episode of *C. jejuni* infection is approximately 100 times higher than the risk in the general population. *Am J Epidemiol* 2001;153:610–14.

Campylobacter infections; *Campylobacter jejuni*; incidence; polyradiculoneuritis

The association between Guillain-Barré syndrome (GBS) and *Campylobacter jejuni* infection has been demonstrated by case reports and case series, many of which have been described in a review article (1), and by case-control studies (2, 3). One of these case-control studies found evidence of ongoing or recent *C. jejuni* infection in 26 percent of GBS cases as compared with 1–2 percent of controls (3). The proportion of GBS cases with evidence of recent *C. jejuni* infection in other studies varies from 14 percent (4) to 88 percent (5). A review of these studies estimated that 30–40 percent of GBS patients had suffered *C. jejuni* infection during the 2 weeks prior to onset of GBS (6).

A biologic mechanism involving molecular mimicry and consequent cross-reaction of the immune response formed against *C. jejuni* antigens with gangliosides (GM1) present in nerves has been suggested and is supported by laboratory studies (7, 8). Host factors, particularly human lymphocyte antigen type, appear to have a role in the pathogenesis of GBS following *C. jejuni* infection (9, 10). Equally, most studies (5, 7, 11), but not all (3), suggest that GBS is more

likely to follow infection with some serotypes of *C. jejuni* than others.

Although understanding of the relation between *C. jejuni* infection and GBS has improved rapidly, the overall risk of GBS following the diagnosis of *C. jejuni* infection has not been measured. One case of GBS was reported following a *C. jejuni* outbreak involving an estimated 865 cases (12). Other published reports on outbreaks of *C. jejuni* do not describe subsequent GBS. In Sweden, there are approximately 30 times as many cases of *C. jejuni* infection reported each year (between 1986 and 1993, the mean was 4,149 per year) (13) as there are cases of GBS (in 1986–1993, the mean was 145 per year) (14, 15). Assuming that one out of every three cases of GBS were related to *C. jejuni* infection and that complete reporting of incident cases occurred for both conditions, the risk of GBS following *C. jejuni* infection would be approximately 1 percent. However, many incident cases of bacterial enteritis are not precisely diagnosed and reported, because patients with enteritis often do not seek medical care and fecal culture is not routine in the investigation of acute gastroenteritis (16, 17). Clinical cases of GBS, a more serious disease, would seem less likely to remain undiagnosed, and the Swedish hospital discharge register has been validated as containing most diagnosed cases (14, 15, 18). This differential level of underdiagnosis means that the real risk is likely to be much lower than 1 percent. Other investigators have used this same approach to estimate the risk of GBS among cases of *C. jejuni* infection in the United States. The most recently published estimate was 1 in 1,058 (6). This method relies on assumptions regarding the number of incident cases of *C. jejuni* infection, which is difficult to estimate accurately (16, 17); the proportion of GBS cases

Received for publication September 1, 1999, and accepted for publication June 8, 2000.

Abbreviation: GBS, Guillain-Barré syndrome.

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that are related to *C. jejuni* infection, which is not precisely known (1, 3–6); and the number of GBS cases occurring per year. Estimation is therefore very sensitive to imprecision in the first two of these three assumptions, reducing the validity of such estimates. To obtain a more reliable estimate of the incidence of GBS in the months after *C. jejuni* infection, we followed a large cohort of infected individuals using Swedish national registers.

MATERIALS AND METHODS

Population registries and matching

Data from the nationwide laboratory reporting system of the Swedish Institute for Infectious Disease Control were used to assemble a cohort of people with *C. jejuni* infection. The cohort comprised cases of *C. jejuni* infection reported to the laboratory reporting system between 1987 and 1995 for which full date of birth and either name or initials were recorded in the institute's computerized database. Although most laboratories do not routinely test *Campylobacter* strains to confirm that they are *C. jejuni*, informal estimates from laboratories which test some strains indicate that well in excess of 95 percent of the strains isolated are *C. jejuni*.

Cases of GBS were detected through the Swedish Inpatient Register. The Inpatient Register records all discharges from hospital inpatient clinics in Sweden. Diagnoses are recorded by modified *International Classification of Diseases* codes. Individual patients are identifiable, because a 10-digit national personal identifier number is included. For the years 1986–1995, we matched the cohort of laboratory-confirmed *C. jejuni* cases with those entries in the Inpatient Register that had *International Classification of Diseases* codes indicating a diagnosis of GBS.

Initial matching was based on matching of dates of birth. If gender was recorded in both files, this was also included as a matching criterion. Matching records were then studied manually, and only those records in which the GBS had occurred between 2 months before and 6 months after the report of *C. jejuni* infection were kept. The full name of each patient with a record in the Inpatient Register that matched a record in the laboratory reporting system register according to the above criteria was then obtained from the National Population Register using the 10-digit identification number. This was compared with the name or initials on the laboratory report. If these were compatible with the two reports belonging to the same individual, the match was considered to represent a possible case of GBS associated with *C. jejuni* infection.

Permission to conduct the study was obtained from the Swedish Data Protection Board.

Follow-up of cases

For each possible case of *C. jejuni*-associated GBS, both the laboratory reporting the *C. jejuni* infection and the clinic reporting the case of GBS were contacted for additional information. Clinical details, including the date of onset of symptoms of GBS and the occurrence of any preceding

symptoms of gastroenteritis, were requested from the clinic that had reported the GBS diagnosis to the Inpatient Register.

Statistical analysis

Exact confidence limits were calculated using the Poisson distribution.

RESULTS

The cohort consisted of 29,567 individuals with laboratory-confirmed *C. jejuni* infection (table 1). Matching by date of birth (and gender, when available) yielded 935 matches. Restriction of the data to GBS cases with admission between 2 months before and 6 months after the report of *C. jejuni* infection reduced this number to 95. Exclusion of persons for whom the name details on the *C. jejuni* infection report were not compatible with the GBS patient's name (obtained from national population registers) further reduced this number to 15.

Patient records were reviewed for all 15 cases. The identity of the patient and the matching was confirmed as correct in each case. For two patients, the initial diagnosis of GBS was later found to be incorrect. In four cases, the diagnosis of *C. jejuni* infection was made because of the occurrence of GBS. These cases were excluded from the study and from the cohort being followed (which was thus reduced to 29,563). A diagnosis of GBS preceded by a diagnosis of *C. jejuni* infection was confirmed for the other nine patients (table 2).

We thus detected nine cases of GBS in a cohort of 29,563 reported cases of laboratory-confirmed *C. jejuni* infection, or one case of GBS among every 3,285 *C. jejuni* cases (95 percent confidence interval: 1,729, 7,210). This can be expressed as 30.4 cases of GBS per 100,000 cases of *C. jejuni* infection (95 percent confidence interval: 13.9, 57.8).

DISCUSSION

The annual incidences of GBS derived from the Swedish Inpatient Register are similar to those that would be expected to occur in a European population (1.45–2.30 per 100,000 per year between 1986 and 1993, age-adjusted to a standard European population) (14, 15). In addition, the Swedish register has been validated as a sensitive method for detecting diagnosed cases of GBS in comparison with hospital records (14, 18). The risk of our having missed incident cases of GBS because of incompleteness of the register is therefore low.

We excluded four cases from the cohort because the diagnosis of *C. jejuni* infection in these cases was due to the occurrence and diagnosis of GBS. In each case, the clinician treating the GBS was aware of the connection between *C. jejuni* infection and GBS and therefore tested for *C. jejuni* infection following the diagnosis of GBS. Figure 1 illustrates why these four individuals were excluded from our study population. Our aim was to follow up a cohort of laboratory-confirmed cases of *C. jejuni* infection (B) to estimate the incidence of GBS in this group (D divided by B).

TABLE 1. Distribution of a cohort of laboratory-reported cases of *Campylobacter jejuni* infection for whom identification details adequate to allow matching with cases of Guillain-Barré syndrome were available, by age group, Sweden, 1987–1995

Age group (years)	Year*								Total
	1987	1988	1989	1990	1992	1993	1994	1995	
0–4	451	358	319	305	463	114	335	378	2,723
5–9	147	111	142	118	156	69	153	129	1,025
10–14	108	107	94	106	127	27	100	82	751
15–19	281	221	257	281	267	61	198	228	1,794
20–24	588	549	631	606	692	233	416	620	4,335
25–29	456	446	550	559	711	310	513	629	4,174
30–34	367	323	337	370	447	184	339	515	2,882
35–39	317	245	286	295	393	144	256	369	2,305
40–44	284	274	304	305	403	106	246	395	2,317
45–49	203	203	227	238	395	159	286	371	2,082
50–54	149	144	186	163	245	125	232	389	1,633
55–59	120	96	129	134	177	74	165	234	1,129
60–64	104	83	118	106	129	49	107	157	853
65–69	54	69	61	78	69	38	94	106	569
70–74	41	56	42	46	67	28	73	101	454
75–79	43	35	30	31	40	8	38	74	299
80–84	23	1	23	13	25	7	33	40	165
≥85	4	1	7	6	15	6	17	21	77
Total	3,740	3,322	3,743	3,760	4,821	1,742	3,601	4,838	29,567

* Reports for 1991 were not registered and therefore could not be included. For 1995, only those cases reported before October 31 were included, since follow-up for later reports would have been less than 2 months and cases of Guillain-Barré syndrome might have been missed.

TABLE 2. Details on the cases of individuals for whom both *Campylobacter jejuni* infection and Guillain-Barré syndrome (GBS) were diagnosed, Sweden, 1987–1995

Sex	Age (years)	Date of hospital admission for GBS	Diagnosis of GBS following <i>C. jejuni</i> infection
Female	60	September 1987	Yes
Male	70	November 1987	GBS diagnosed first
Female	62	May 1988	Yes
Male	68	August 1988	Yes
Female	61	October 1988	Yes
Female	25	March 1989	GBS diagnosis not correct
Male	53	September 1989	GBS diagnosis not correct
Female	33	February 1993	Yes
Male	40	August 1994	GBS diagnosed first
Male	64	September 1994	Yes
Male	6	September 1994	GBS diagnosed first
Male	22	December 1994	Yes
Female	2	May 1995	GBS diagnosed first
Female	77	June 1995	Yes
Female	58	September 1995	Yes

The majority of incident cases of *C. jejuni* infection in the Swedish population during the study period are likely to have gone undiagnosed (A minus B). Some of these patients with undiagnosed cases are likely to have developed GBS (C). It is not appropriate that these cases should then enter the study population—that they should move from C to D. This would bias the result toward overestimation of the incidence of GBS among persons with *C. jejuni* infection.

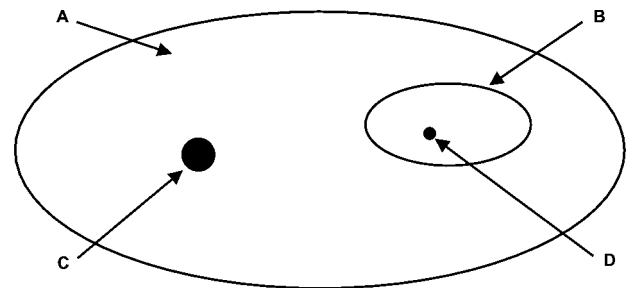


FIGURE 1. Subsequent Guillain-Barré syndrome among patients with *Campylobacter jejuni* infection in Sweden, 1987–1995. The diagram illustrates all cases of *C. jejuni* infection in the Swedish population during the study period (A), the study cohort of cases with reported laboratory-confirmed *C. jejuni* infection (B), and subsequent Guillain-Barré syndrome among unreported (C) and reported (D) cases of *C. jejuni* infection.

We included cases of GBS occurring up to 2 months before the report of *C. jejuni* infection, to allow for potential delays in our laboratory reporting system (19). The follow-up period for detection of GBS after the *C. jejuni* report date was 6 months for most of the cohort, but for *C. jejuni* cases reported between July and October of 1995, the follow-up period was shorter (2–6 months). A mean interval between symptoms of *C. jejuni* infection and the onset of GBS of 9 days (range, 4–20; *n* = 18) was reported in one study (3), and a mean of 10 days (range, 1–23; *n* = 28) was reported

in a review of case series (1). We therefore think that inclusion of *C. jejuni* cases with at least 2 months' follow-up in our cohort was appropriate and did not lead to a loss of sensitivity in the detection of subsequent GBS. Exact information on the date of onset of symptoms of *C. jejuni* infection was not available for all of our cases, although records did indicate that symptoms of gastroenteritis were present before the onset of symptoms of GBS. In seven of the nine confirmed cases, the date of fecal sampling was clearly recorded. The sample preceded admission to hospital with GBS by a mean of 11 days (median, 9; range, 5–26) in these cases, which is consistent with earlier reports. Our study is therefore limited in terms of the amount of information it adds to the estimation of the period between infection or symptoms of gastroenteritis and subsequent GBS.

The presence of good identifier data and the individual follow-up of each match helped us avoid the risk of false matches, so that matched records from each source did represent the same person in each case. Thus, the sensitivity and specificity of the methods used in this study impart a reliable estimate of the incidence of GBS following laboratory-confirmed *C. jejuni* infection.

This study was based on diagnosed cases of *C. jejuni* infection, which were likely to have been symptomatic. It is uncertain whether asymptomatic *C. jejuni* infection is followed by the same incidence of GBS. Some patients with GBS related to *C. jejuni* infection do not recall having symptoms of gastroenteritis; five of 19 *C. jejuni*-positive GBS patients recalled no symptoms of gastroenteritis in one study (20), and eight of 27 recalled no symptoms in another study (3). Whether the risk is higher, lower, or the same among symptomatic cases of *C. jejuni* infection compared with cases without symptoms of gastroenteritis is uncertain. The risk may also vary for populations of substantially different genetic constitutions, since human lymphocyte antigen type may be important in this respect (9, 10). In this study, the estimate was for the range of serotypes found throughout Sweden over 9 years and the range experienced by Swedes traveling abroad (approximately 50 percent of *C. jejuni* cases reported in Sweden are acquired outside the country). A wide variety of serotypes is likely to have been involved. For populations with very different prevailing serotypes, the risk may vary somewhat, since some Penner (5, 7, 11, 21) and Lior (22) serotypes appear to confer a higher risk than other serotypes. Follow-up of outbreaks will provide the best opportunity to estimate serotype-specific risks (12, 23).

Another host factor contributing to the risk of GBS following *C. jejuni* infection may be age. The numbers of cases in this study were too small for us to draw any conclusions in this regard. However, the differences in rates of GBS following *C. jejuni* infection among different age groups are striking (tables 1 and 2). In children and adolescents, no cases of GBS were found. Among the 20,856 adults aged 20–59 years, three cases were detected, giving a rate of 14 per 100,000, while the six cases occurring in the 2,417 people over age 59 represented a rate of 248 per 100,000. This suggests that GBS following *C. jejuni* infection may be particularly common among the elderly, although further study is clearly needed.

Accepting the caveats regarding generalizability, this study estimates the incidence of GBS following symptomatic *C. jejuni* infection by an unknown serotype to be 30.4 per 100,000. On the basis of the current study and other published work (1, 3), the excess risk of GBS appears to be confined to the 2-month period following *C. jejuni* infection. This makes it appropriate to calculate attributable risk based on the background incidence expected for a 2-month period. In our cohort, the expected incidence during a 2-month period in the absence of *C. jejuni* infection would have been only 0.3 per 100,000 people (14, 15) as compared with the 30.4 per 100,000 observed; this yields an attributable risk of 30.1 cases of GBS per 100,000 cases of laboratory-confirmed *C. jejuni* infection. Expressed as a relative risk, the incidence of GBS during the 2 months following a symptomatic episode of *C. jejuni* enteritis would be approximately 100 times higher than the risk in the background population.

Some authors have argued that the severity of GBS means that, although it is rare, this complication of *C. jejuni* infection adds considerably to the total disease burden due to the infection (24). The result of this study permits the establishment of a more firm quantitative foundation for assessment of the importance of GBS relative to other clinical manifestations of *C. jejuni* infection. It confirms that GBS is an important but rare complication of *C. jejuni* infection.

ACKNOWLEDGMENTS

Dr. Noel McCarthy received support from the European Commission Directorate General 5 through the European Programme for Intervention Epidemiology Training.

The authors thank Leif Forsberg for his work on matching cases from the two registers, Temmam Asbai for providing the data from the Swedish Institute for Infectious Disease Control register, and Johan Lindbäck for obtaining full names from the population register. The authors also thank the laboratory staff and clinicians who provided answers to their questions on the cases identified.

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