The risk of Guillain–Barré syndrome following infection with *Campylobacter jejuni*

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SUMMARY

To estimate the incidence of Guillain-Barré syndrome (GBS) following *Campylobacter jejuni* infection (CI) we studied three populations where outbreaks of CI had occurred involving an estimated 8000 cases. No case of GBS was detected in the 6 months following the outbreaks in the local populations. The point estimate for the risk of GBS following CI estimated in this study was 0 in 8000 (95 % confidence interval 0–3).

INTRODUCTION

The association between Guillain–Barré syndrome (GBS) and *Campylobacter jejuni* infection (CI) has been demonstrated by case reports and case series, many of which have been gathered together in a review [1], and case-control studies [2, 3]. The largest such study showed evidence for ongoing or recent CI in 26 % of GBS cases compared to 1–2 % of controls [3]. Laboratory research suggests a biological mechanism through cross-reaction of the immune response formed against campylobacter antigens with gangliosides (GM1) present in nerves [4, 5]. HLA typing of GBS has found an excess of HLA-DQB1*03 among those with evidence of preceding CI compared to those with no evidence of recent CI [6], while Japanese cases of CI associated GBS had the HLA-B35 antigen at a much higher rate than the general population [7]. These studies suggest that people with certain HLA types may have a higher risk of GBS following CI. Some reports [4, 8, 9], but not all [3], suggest that certain campylobacter serotypes are more strongly associated with GBS than others. The magnitude of the risk GBS following CI infection has not been

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estimated. One case of GBS was reported following a CI outbreak involving an estimated 865 cases [10]. We have been unable to find any other published studies allowing estimation of the risk.

MATERIALS AND METHODS

The study population (denominator data)

Three large outbreaks of CI, all waterborne, have been detected and studied in Sweden [11–13] (Table 1). The investigation of each involved a cross-sectional survey by post and/or telephone within the affected municipalities using clinical case definitions. In one a door-to-door interview was also conducted in part of the area affected. These outbreak investigations allowed an estimate of the number of cases affected within well defined geographical and administrative areas. Each outbreak was characterized by a high attack rate in a relatively small population during a short time period, and involved all age groups.

Detection of GBS cases (numerator data)

The National Hospital Discharge Register (NHDR) records all discharges from hospital in-patient clinics

Table 1. *Outline of the three outbreaks of CI giving rise to the study population*

Outbreak location	Grums-Vålberg	Kramfors	Marks
Dates of onset of illness	1–15 October 1980	21–26 May 1994	24–29 May 1995
Total population	14 500	10 000	19 000
Cases of gastroenteritis	2086	2500	3500
Campylobacter positive faecal samples	221 of 263 (84%)	71*	60*
Other agent cultured	0 of 45	0*	0*
Penner serotype†	6, 7	34, 27	16
Lior serotype	Not tested	4	1
Percentage of the population included in the outbreak investigation	5%	6%	20%

* Exact number of patient samples tested not available. All samples tested were examined for routine faecal pathogens including *Salmonella*, *Shigella*, and *Yersinia* sp. as well as *Campylobacter* sp.

† Penner serotypes refer to the serotypes isolated from patients during the outbreak. Only 1, 5, and 2 isolates from the Grums, Kramfors, and Marks outbreaks respectively were fully serotyped. These typed strains were identical for isolates within each outbreak.

in Sweden. Diagnoses are recorded by modified ICD codes. Individual patients are identifiable since a 10 digit personal identifier number is included. The NHDR has been validated as a sensitive method to detect cases of GBS [12–14]. We defined a probable case as any person with (i) a discharge record including an ICD code for GBS during the 6 month period after an outbreak and (ii) an address code for either the outbreak municipality or an adjacent municipality. A similar case definition, but using the 6 month period starting 1 year before the outbreak occurred, was used to obtain a background rate for comparison. Cases with an ICD code for GBS as either a main or secondary diagnosis were included to increase sensitivity.

Verification of GBS cases

The addresses of these probable cases with an address code for the municipality of the outbreak or an adjacent one were verified using the population register of the Swedish Tax Office. Patient records were checked at the treating hospital to verify the clinical details of any case with a verified address in the outbreak municipality under follow up for that period.

RESULTS

We identified one case within one of the three municipalities during the periods studied and nine in adjacent municipalities. Review of the patient record of the single case indicated that the person had been diagnosed with GBS 2 years earlier and was admitted to hospital for entirely different reasons. We therefore detected no case of GBS in either the combined periods of follow up after the outbreaks of CI or in the 6 month periods starting 1 year before each outbreak. Exact calculation using the binomial distribution gave a 95% confidence interval of 0–3 cases of GBS per 8000 cases of CI.

DISCUSSION

Following three waterborne outbreaks of CI affecting about 8000 people no cases of GBS were identified. Applying the national incidence figures for GBS to the combined study population leads to an expected incidence of 0·4 cases per 6-month period.

The follow-up period of 6 months should have been sufficient to identify linked cases of GBS. A mean interval between the symptoms of CI and the onset of GBS of 9 days (range 4–20) was reported in one study (n = 18) [3], and a mean of 10 days, (range 1–23) in a review of case series (n = 28) [1]. The numbers of cases recorded per year on the NHDR are similar to those expected for a European population suggesting that substantial underdiagnosis was unlikely [14–16].

Our study gives a very low risk estimate for GBS following CI, with a maximum likelihood estimate of 0 per 8000 and 95% confidence interval of not more than 3 cases of GBS following 8000 cases of CI. This study was based on just three outbreaks. Only a few campylobacter serotypes may have been involved. The rate of GBS may vary by serotype [3, 4, 8, 9]. The follow up of a large cohort of people with CI due to

a broad range of serotypes would allow a more definitive average risk estimate.

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