Campylobacter jejuni Strains from Patients with Guillain-Barré Syndrome

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Guillain-Barré syndrome (GBS), an acute demyelinating peripheral neuropathy, may be triggered by an acute infectious illness; infection with *Campylobacter jejuni* is the most frequently reported antecedent event. In Japan, O:19 is the most common serotype among GBS-associated *C. jejuni* strains. To determine whether serotype O:19 occurs among GBS-associated strains in the United States and Europe, we serotyped seven such strains and found that two (29%) of seven GBS-associated strains from patients in the United States and Germany were serotype O:19. To determine whether GBS-associated strains may be resistant to killing by normal human serum (NHS), we studied the serum susceptibility of 17 GBS- and 27 enteritis-associated strains (including many O:19 and non-O:19 strains) using *C. jejuni* antibody positive (pool 1) or negative (pool 2) human serum. Using pool 1 serum we found that one (6%) of 18 serotype O:19 strains compared with 11 (42%) of 26 non-O:19 strains were killed; results using pool 2 serum were nearly identical. Finally, 8 O:19 and 8 non-O:19 strains were not significantly different in their ability to bind complement component C3. Serotype O:19 *C. jejuni* strains were overrepresented among GBS-associated strains in the United States and Germany and were significantly more serum-resistant than non-O:19 strains. The mechanism of this resistance appears unrelated to C3 binding.

Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy characterized by an immunologic attack upon peripheral nerve myelin (1,2). The trigger for this immune attack is unknown; however, GBS is frequently preceded by an acute infectious illness (3). In recent years, infection with *Campylobacter jejuni* has emerged as one of the most common antecedent events associated with GBS. Up to 40% of patients with GBS have culture or serologic evidence of *C. jejuni* infection when neurologic symptoms begin (4-6). The many variants of GBS—including acute motor axonal neuropathy, acute inflammatory demyelinating neuropathy, and Miller Fisher syndrome—have also been associated with preceding *C. jejuni* infection (7-9).

C. jejuni infections are common in the United States, affecting approximately 1% of the population each year (10). Typically, they cause a self-limited gastrointestinal illness characterized by diarrhea, abdominal pain, and fever. However, approximately 1 in 2,000 *C. jejuni* infections may be complicated by GBS (11). Because *C. jejuni* infections occur far more commonly than GBS, either host (12) or strain (5,13) characteristics may determine which infected persons contract GBS. Several reports from Japan showed that a particular serotype, O:19, was overrepresented among *C. jejuni* strains isolated from GBS patients (5,13). Among 12 Japanese patients with GBS and culture-confirmed *C. jejuni* infection, 10 (83%) were infected with strains of O:19, a serotype that accounts for only 2% of randomly selected *C. jejuni* isolates in Japan (5). However, in England, none of four *C. jejuni* strains isolated from patients with GBS were serotype O:19 (6). Other *Campylobacter* serotypes predominate among GBS patients in other parts of the world. All nine *C. jejuni* strains isolated from GBS patients in South Africa were serotype O:41 (14);

this serotype accounts for fewer than 2% of isolates from South African children with uncomplicated enteritis. With Lior typing (a serotyping system based upon heat-labile antigens), all four GBS-associated *C. jejuni* strains in Germany were serotype O:11 (15).

Whether the predominance of O:19 strains among GBS patients is limited to Japan is not clear. Furthermore, the reason for the O:19 overrepresentation among Japanese GBS strains is unknown, but their resistance to host bacterial clearance mechanisms is one possibility. *C. jejuni* strains vary in their susceptibility to the bactericidal activity in normal human serum (NHS) (16). Bacteria that are more resistant to nonspecific serum killing may elicit more extensive specific responses to eliminate the organism; such elicited immune responses may have the potential of greater tissue injury and myelin damage.

To determine whether *C. jejuni* serotype O:19 is an important cause of GBS outside Japan, we serotyped GBS-associated strains from the United States and Germany. To investigate the immunologic response to GBS-associated *C. jejuni* strains, we performed two additional sets of experiments. First, we examined the susceptibility of *C. jejuni* strains to NHS. Our hypothesis was that GBS-associated *Campylobacter* strains, more specifically O:19 strains, are more serum-resistant than those from patients with uncomplicated enteritis. To further characterize the mechanism of resistance, we determined whether *C. jejuni* strains isolated from GBS patients differ in their capacity to bind complement component C3.

Statistical Analysis

We determined mean values, standard deviations, odds ratios, p-values, paired T-tests, 95% confidence limits, and interquartile ranges. Software included Lotus 123 and EpiInfo (a statistical software package designed by the Centers for Disease Control and Prevention [CDC]).

Serotyping of Strains

Seven GBS-associated strains were serotyped with the O (formerly heat-stable) serotyping scheme of Penner and Hennessy (17) and the heat-labile serotyping scheme of Lior (18). Serotyping was conducted (19) at the CDC *Campylobacter* Reference Laboratory. A GBS-associated strain was defined as one isolated from a patient with GBS (n = 6) or from a patient infected during an outbreak in which at least one infected person contracted GBS (n = 1). Four strains were from patients in the United States, and three were from patients in Germany; four of these were isolated from women.

Serotype O:19 was present in one of four U.S. GBS-associated *C. jejuni* isolates and one of three German isolates. Thus, 2 (29%) of 7 GBS-associated *C. jejuni* isolates from patients in the United States and Germany were O:19. The O and heat-labile serotypes of the seven GBS-associated strains are shown in Table 1.

Serum Bactericidal Assays

We studied 44 GBS- and enteritis-associated strains from all over the world. We divided *C. jejuni* isolates into two major groups. Group 1 (17 GBS-associated strains) was divided into two subgroups. Subgroup 1A (GBS-associated/type O:19) consisted of seven *C. jejuni* O:19 isolates: three from the United States, three from Japan, and one from Germany. Subgroup 1B (GBS-associated/non-O:19 serotype) consisted of 10 *C. jejuni* isolates with serotypes other than O:19: three from the United States, two from Germany, and five from England. Group 2 (27 enteritis-associated strains from patients with uncomplicated enteritis but no known GBS association) was also divided into two subgroups. Subgroup 2A (not GBS-associated/type O:19) consisted of 11 *C. jejuni* O:19 isolates: 10 from the United States and one from Japan. Subgroup 2B (not GBS-associated/non-O:19 serotype) consisted of 16 *C. jejuni* isolates from U.S. patients with serotypes other than O:19. Serum-resistant *C. fetus* strain 23D and its spontaneous serum-susceptible mutant, 23B, were used as controls (20).

Strains were grown on trypticase soy blood agar plates (BBL Cockeysville, MD, USA) at 37°C for 48 hours in an incubator containing 10% CO_2, 5% O_2, and 85% N_2. The bacteria were harvested in 0.15M saline and centrifuged at 8,000 g for 15 minutes. The supernatant was discarded, the pellet was resuspended in 300 µl of saline, and 10-fold serial dilutions were performed in saline. From the 10^{-4}, 10^{-5}, and 10^{-6} dilutions, 400 µl aliquots of cells were added to 1.2 ml of Hanks balanced salt solution (HBSS).

Two sources of NHS were used in these assays. Pool 1 consisted of serum from five healthy adults that was pooled, aliquotted, and frozen at -70°C. The level of *C. jejuni* antibodies in pool 1 serum was determined by enzyme-linked immunosorbent assay (ELISA) (4). The optical

Table 1. Serotypes of Guillain-Barré syndrome–associated *Campylobacter jejuni* strains from the United States and Germany

Strain designation CDC[c]	Vanderbilt[d]	(O)[a]-sero-type	(HL)[b]-sero-type	Location	Age/sex
D459	93-002	19	77	Florida	79F
D2769	93-006	2	4	Maine	F
D4262	84-158	19	84	Germany	59F
D4266	84-196	2	4	Germany	24M
D4267	84-197	8,17	40	Germany	71F
D4271	86-381	2	4	Wisconsin	30M
D4808	93-001	1	4	Washington	57M

[a]O = heat-stable.
[b]HL = heat-labile.
[c]Designated strain number assigned by the Centers for Disease Control and Prevention *Campylobacter* Reference Laboratory.
[d]Designated strain number in the Vanderbilt *Campylobacter/Helicobacter* strain collection.

density ratio (ODR) for immunoglobulin G (IgG) was 5.14; the ODR for IgM was 0.66. Documentation of previous *C. jejuni* infection was not required to be included in this pool. In contrast, pool 2 consisted of serum from two healthy adults with only low-titer antibody. The ODR for pool 2 serum in the IgG assay was 0.37; and the ODR in the IgM assay was 0.30. As a control, the NHS was heated to 56°C for 30 minutes (heat inactivated NHS [HINHS]) to ablate all complement activity.

The assay to determine susceptibility to NHS was performed in sterile, disposable 96-well microtiter U-bottom plates (Falcon MICROTEST III, Becton Dickinson & Co., Franklin Lakes, NJ, USA). From each of the bacterial suspensions, a 150 µl aliquot was added to duplicate wells. In addition, 50 µl of NHS or HINHS (diluted to 40% with HBSS) was added; the final serum concentration in the suspension was 10%. After the assay plate was incubated at 37°C for 1 hour, 50 µl of the suspension from each well was poured onto blood agar plates and incubated for 48 hours; the number of CFUs was then calculated. The difference between the counts for cells incubated with NHS and HINHS was expressed as median $\log_{10}$ kill for each strain; greater than 1 $\log_{10}$ kill was considered a serum-susceptible strain (21). If less than 1 $\log_{10}$ kill occurred, the strain was considered serum-resistant. The identical procedure was performed using pool 1 and pool 2 serum.

The resistance of the 44 *C. jejuni* strains studied to killing by NHS is shown in Table 2. Of these strains, 12 (27%) were resistant to killing by *C. jejuni* antibody-positive pool 1 serum and 10 (23%) were resistant to killing by *C. jejuni* antibody-negative pool 2 serum; thus, as described previously (22), antibodies to *C. jejuni* had little impact on serum-killing. The GBS-associated strains were no more likely to be resistant to serum-killing than were the strains from patients with uncomplicated enteritis. However, O:19 strains were significantly more likely than other *C. jejuni* serotypes to resist serum-killing, regardless of GBS-association and serum pool used (Table 2). In serum pool 1, only 1 of 18 O:19 strains was serum-susceptible compared with 11 (42%) of 26 non-O:19 strains (odds ratio = 12.5, p = 0.008). Similarly, in serum pool 2, no O:19 strain was serum-susceptible compared with 10 (38%) of the non-O:19 isolates.

[125]I-C3 Binding Assays

Eight strains from Group 1 (four randomly selected from each subgroup) and eight from Group 2 (four randomly selected from each subgroup) were grown on blood agar plates as described above. *C. fetus* strains 23D and 23B again served as controls and the assays were conducted (21). In brief, bacteria from each plate were harvested in 1.5 ml of HBSS and were centrifuged at 8,000 g for 15 minutes; the pellet was resuspended in 0.5 ml HBSS and adjusted to OD_{450} = 3.0. For each strain studied, a suspension of 4 µl ^{125}I-C3 (with 20,000 cpm to 65,000 cpm) and 2.5 µl of either NHS or HINHS from pool 2 and 100 µl of the bacteria-HBSS suspension were incubated at 37°C for 15 minutes. ^{125}I-C3 was prepared in the laboratory of one of the authors (RGW) (21). The suspensions were then centrifuged twice at 175xg for 5 minutes, the pellet was resuspended in HBSS, and the supernatant was discarded. The bottom 5 mm (containing the pellet) of each tube was clipped, and emissions were determined in a gamma counter. The counts in the negative control mixtures containing HINHS were subtracted from the NHS counts. An assay was considered valid only if the net pellet counts (NHS minus HINHS) for control strain 23B were at least four times higher than for 23D. To control for nonspecific binding, the counts for each strain studied were expressed as the ratio of net counts relative to the serum susceptible control (23B). Each strain was assayed two to four times.

Mean binding of serum-susceptible control strain 23B was 497 cpm, whereas mean binding of serum-resistant control strain 23D was 54. The

Table 2. Susceptibility of *Campylobacter jejuni* strains to killing by normal human serum (NHS)

Illness	O serotype	No. of strains studied	No. (%) with >1 log kill[a,b]		Median log kill (interquartile range)	
			Pool 1[c]	Pool 2[c]	Pool 1	Pool 2
GBS[d]	19	7	1 (14)	0 (0)	0.53 (0.18-0.63)	0.39 (0.08-0.52)
Enteritis	19	11	0 (0)	0 (0)	0.37 (0.09-0.47)	0.48 (0.29-0.50)
GBS	non-19	10	3 (30)	3 (30)	0.70 (0.44-1.18)	0.43 (0.03-1.32)
Enteritis	non-19	16	8 (50)	7 (44)	0.90 (0.24-2.00)	0.59 (0.35-2.53)
All	19	18	1 (6)	0 (0)	0.38 (0.17-0.58)	0.45 (0.23-0.52)
All	non-19	26	11 (42)	10 (38)	0.70 (0.26-1.86)	0.54 (0.17-2.27)

[a]Bacterial suspensions were incubated in either NHS or heat inactivated NHS at 37°C for 1 hr as described in text, and net CFU (NHS minus HINHS) determined. Values greater than 1 $\log_{10}$ kill were considered to denote a serum-susceptible strain.
[b]Comparison of O:19 strains with non-O:19 strains: Pool 1, odds ratio = 12.5, p = 0.008; Pool 2, odds ratio = undefined, p = 0.003.
[c]Pool 1 consists of *C. jejuni*-antibody positive serum from five healthy adults; Pool 2 consists of *C. jejuni*-antibody negative serum from two healthy adults.
[d]GBS = Guillain-Barré syndrome.

mean ratio of C3-binding for strain 23D to 23B of 0.114 was as expected (21). In contrast, the mean ratio for C3 binding to *C. jejuni* strains in comparison with strain 23B was 0.022 to 0.464 (mean 0.216). The eight O:19 strains were not significantly different from the eight non-O:19 strains in their ability to bind ^{125}I-C3 (Table 3).

Conclusion

This study of GBS patients in the United States and Germany confirms the observation made in Japan that serotype O:19 is overrepresented among patients with *C. jejuni*-induced GBS. Of 298 randomly collected *Campylobacter* isolates from patients with enteritis in the United States, only 3% were serotype O:19 (19). A similarly low prevalence of O:19 strains is found in all parts of the world, including North and South America, Asia, and Europe (5,6,19,23). Although specific serotyping surveys have not been done in Germany, it is unlikely that serotype O:19 is more frequent among German *C. jejuni* isolates. Thus, the GBS-associated strains in our study were more than 11 times as likely to belong to this serotype (p = 0.03). Although the association among GBS and *C. jejuni* serotype O:19 was not as marked as in Japan (where more than 80% of GBS-associated isolates are O:19), this serotype clearly is overrepresented among GBS-associated strains in other countries. We conclude that the association of O:19 strains with GBS is not just a local phenomenon in Japan but likely reflects a fundamental characteristic of O:19 strains. O-serotype 2 and heat-labile serotype 4, which were common among the GBS strains, are commonly represented among

infected persons in the United States (23).

Despite the frequency of *Campylobacter* infections in GBS patients, such strains are difficult to obtain for several reasons. First, in most *C. jejuni*-infected patients, stools are clear before neurologic symptoms begin. Second, most neurologists do not culture stool samples when GBS is first diagnosed. And finally, even if a stool culture is ordered and *Campylobacter* is present, few microbiology laboratories save their isolates; by the time the case is reported, the strain has been discarded. Thus, these seven strains represent one of the largest collections of GBS-associated strains described. Additionally, these are likely to be representative of the population of GBS-associated *C. jejuni* strains. Unless serotype O:19 strains persist in stools longer, are more easily cultured, or are less likely to be discarded by microbiology laboratories (and no data support any of these possibilities), these strains probably are not different in any systematic way from other GBS-associated isolates.

Most *C. jejuni* strains are susceptible to killing by human serum (22), but because we studied highly selected strains (most either serotype O:19 or from GBS patients), a high proportion of strains in this investigation were resistant. In this context, the finding that *C. jejuni* strains from GBS patients were no more likely than the strains from patients with uncomplicated enteritis to be serum resistant is not surprising. Even when the analysis was limited only to serotype O:19 strains, no differences were found between GBS- and enteritis-associated strains. However, serotype O:19 strains were substantially less serum-

Table 3. Comparison of ^{125}I-C3 binding to *Campylobacter jejuni* strains

Measure	Serotype of *C. jejuni* strain	
	O:19 (n = 8)	non-O:19 (n = 8)
Counts per minute[a]	85 +/-51	98 +/- 48
Mean binding ratio[b]	0.187 +/- 0.116	0.245 +/- 0.130

[a]Bacterial cells were incubated with pool 2 normal human serum or heat inactivated normal human serum and ^{125}I-C3 (mean 40,416 [range 20,234-63,503]. cpm) at 37ºC for 15 minutes. The cells were centrifuged and washed; net (NHS minus HINHS) [125]I binding was measured as counts per minute. p-value = 0.20 (paired T-test, 1-tailed).
[b]The mean binding ratio is an average of the ratio of the net counts for each study strain relative to the net counts of the serum-susceptible control (23B). p-value = 0.31 (paired T-test, 1-tailed).

susceptible than strains of other serotypes and were 12 times as likely to be serum-resistant. Although serotype O:19 represents only a small percentage of *C. jejuni* strains from patients with uncomplicated enteritis in the United States or Japan, it is the most common serotype identified in GBS patients in both locales. The relatively small variation in serum susceptibility of the O:19 strains is consistent with the close genetic relationship observed among these strains (24).

To better understand the basis for the relative serum-resistance among the O:19 strains, we compared their ability to bind C3 in relation to non-O:19 strains. Because C3 binding occurs after activation by either the alternative or classical complement pathways, it is a screen for differences in these early steps. The serum-resistance of *C. fetus* is explained by the inability of C3 to bind to the cell surface (25). In contrast, C3 binding is normal in serum-resistant *Salmonella,* but the C5-9 membrane attack complex does not insert properly (26). In the present study, the lack of substantial C3 binding differences among O:19 and non-O:19 *C. jejuni* strains suggests that the early steps in complement activation are similar among strains. However, clear differences in serum-susceptibility bespeak either rapid inactivation of C3 or reduced assembly or function of the membrane attack complex in the more resistant strains. Future studies should address this point.

The increasing awareness of the importance of *C. jejuni* infection in triggering GBS is another example of how previously well-described diseases have emerged as sequelae of acute infectious illnesses. This study attempts to begin to characterize the nature of this association; however, there is much to learn about how an acute gastrointestinal infection results in ascending paralysis. One fact is quite clear: many more people are infected with *C. jejuni* than contract GBS subsequently. Perhaps some persons are predisposed to contracting GBS after infection with campylobacters that might cause only uncomplicated enteritis in another patient. Conversely, as we have suggested in this paper, some strains may be more likely than others to trigger GBS. No associations between human leukocyte antigen (HLA) types and GBS have been found (27,28). However, in Great Britain and Japan, an association between HLA type and *C. jejuni*-associated GBS has been suggested (9,29). Perhaps some combination of familial susceptibility, HLA type, strain serotype, or other host or strain characteristics together play a role in the pathogenesis of *C. jejuni*-induced GBS.

The relative serum-resistance of O:19 strains correlates with mechanism. Furthermore, the relevance of these in vitro assays to the susceptibility of organisms in vivo cannot be known with certainty. We speculate that the relative insensitivity of these strains to the lytic effects of complement allows them to trigger a heightened specific immunologic response. We further speculate that this heightened immuno-logic response leads to injury of peripheral nerve structures. Since only a small fraction of infections caused by *C. jejuni* O:19 lead to GBS (estimated incidence 1 in 158) (30), additional factors also must be involved in vivo.

Acknowledgments

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Perspectives

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