

## CAMPYLOBACTER JEJUNI INFECTION AND GUILLAIN-BARRÉ SYNDROME

JEREMY H. REES, PH.D., M.R.C.P., SARA E. SOUDAIN, B.SC., NORMAN A. GREGSON, PH.D.,  
AND RICHARD A.C. HUGHES, M.D.

**Abstract** *Background.* Although infection with *Campylobacter jejuni* is recognized as a common antecedent of the Guillain-Barré syndrome, the clinical and epidemiologic features of this association are not well understood.

*Methods.* We performed a prospective case-control study in a cohort of patients with Guillain-Barré syndrome (96 patients) or Miller Fisher syndrome (7 patients) who were admitted to hospitals throughout England and Wales between November 1992 and April 1994. Bacteriologic and serologic techniques were used to diagnose preceding *C. jejuni* infection.

*Results.* There was evidence of recent *C. jejuni* infection in 26 percent of the patients with Guillain-Barré or Miller Fisher syndrome, as compared with 2 percent of household controls and 1 percent of age-matched hospital controls ( $P < 0.001$ ). Of the 27 patients with *C. jejuni* infection, 19 (70 percent) reported having had a diarrheal

illness within 12 weeks before the onset of the neurologic illness. No specific serotypes were associated with Guillain-Barré syndrome. *C. jejuni* infection was slightly more common in men ( $P = 0.14$ ) and was more likely to be associated with a pure motor syndrome and a slower recovery ( $P = 0.03$ ). The patients with preceding *C. jejuni* infection were more likely to have acute axonal neuropathy or axonal degeneration in association with acute inflammatory demyelinating polyradiculoneuropathy, and they had greater disability after one year ( $P = 0.02$ ). *C. jejuni* infection was significantly associated with a poor outcome even after correction for other factors associated with a poor prognosis.

*Conclusions.* Infection with *C. jejuni* often precedes the Guillain-Barré syndrome and is associated with axonal degeneration, slow recovery, and severe residual disability. (N Engl J Med 1995;333:1374-9.)

GUILLAIN-BARRÉ syndrome is the most common cause of acute neuromuscular paralysis,<sup>1</sup> yet its cause and pathogenesis are unknown. In approximately two thirds of patients, neuropathic symptoms follow an infection — often a mild, undiagnosed respiratory or gastrointestinal illness. The organism that has most frequently been described in association with Guillain-Barré syndrome is *Campylobacter jejuni*, a gram-negative rod that is now the most common cause of bacterial gastroenteritis in developed countries. Although there has been a plethora of case reports and studies documenting the association,<sup>2</sup> the specific clinical and epidemiologic features are not well known. In addition, there is controversy about whether those with preceding *C. jejuni* infection have a more severe form of the Guillain-Barré syndrome.<sup>3-5</sup> We therefore undertook a prospective case-control study of over 100 patients with the syndrome and systematically examined all the patients and controls for evidence of *C. jejuni* infection, using bacteriologic and serologic techniques. In addition, all patients were followed for one year to determine the effect of *C. jejuni* infection on prognosis.

### METHODS

#### Study Population

Patients with Guillain-Barré or Miller Fisher syndrome were recruited between November 1992 and April 1994 from district general and teaching hospitals throughout England and Wales. The diagnosis of Guillain-Barré syndrome was defined clinically according to the criteria of Asbury and Cornblath.<sup>6</sup> After informed consent was obtained, clinical data were collected. Two controls were recruited for each patient wherever possible, one being a member of the patient's

household (household control) and the other being an age-matched (within 10 years) patient admitted to the same hospital at about the same time as the patient with Guillain-Barré syndrome (hospital control) who did not have an acute neuropathy or diarrheal illness. All the subjects were asked about recent infections, vaccinations, or surgical procedures with the use of a structured questionnaire. To describe the patients' worst deficits at the peak of their illness, we used an ordinal scale to grade five aspects of their neurologic states, as follows: *Greatest overall disability* (0 to 6): 0, the patient is healthy, with no signs or symptoms of Guillain-Barré syndrome; 1, the patient has minor symptoms or signs and is capable of running; 2, the patient is able to walk 5 m across an open space without assistance, a walker, or a cane, but is unable to run; 3, the patient is able to walk 5 m across an open space with the help of one person and a waist-level walker or crutches; 4, the patient is chairbound or bedbound and unable to walk as described for grade 3; 5, the patient requires assisted ventilation for at least part of the day or night; and 6, the patient is dead. *Greatest arm weakness* (0 to 4): 0, use of arm is normal; 1, the patient has minor symptoms or signs, but is able to put hand on top of head when sitting with head upright and able to oppose thumb to each fingertip; 2, the patient is either able to put hand on top of head when sitting with head upright or able to oppose thumb to each fingertip, but not both; 3, the patient has some arm movement, but is unable to perform either of the tasks in grade 2; and 4, the patient has no arm movement. *Poorest sensory ability* (0 to 3): 0, sensory ability is normal; 1, the patient has symptoms but no signs; 2, the patient has anesthesia or analgesia of fingers or feet; and 3, the patient has anesthesia or analgesia to elbows or knees or worse. *Poorest facial and bulbar condition* (0 to 3): 0, the patient's condition is normal; 1, the patient has minor symptoms or signs; 2, the patient has moderate weakness; and 3, the patient has complete paralysis.

Blood and up to three stool samples were collected from each patient and control. The subsequent progress of all the patients was monitored by telephone, and those who were unable to walk independently at the end of one year were reexamined and tested electrophysiologically. The study was approved by the local ethics committee.

#### Electrophysiologic Data and Classification

Electrophysiologic data were gathered from the case notes or from nerve-conduction studies performed by one of us. These were carried out at the various hospitals with the use of conventional recording techniques. Because of the lack of uniformity of the electrophysiologic data collected and the fact that investigations were often incomplete, we classified patients electrophysiologically according to three categories on the basis of the overall interpretation of the data. We reached a consensus after discussing the classifications among our

From the Department of Neurology (J.H.R., S.E.S., R.A.C.H.) and the Division of Anatomy and Cell Biology (N.A.G.), United Medical and Dental Schools, Guy's Hospital, London. Address reprint requests to Dr. Rees at the Department of Neurology, Royal Free Hospital, Hampstead, London NW3 2QG, United Kingdom.

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selves and with two experienced neurophysiologists. Patients were classified as having acute inflammatory demyelinating polyradiculoneuropathy when there was evidence that conduction was slowed or blocked proximally or distally, according to the criteria of Albers et al.<sup>7</sup> The presence of axonal degeneration in association with acute inflammatory demyelinating polyradiculoneuropathy was inferred when there was either additional electromyographic evidence of denervation (fibrillations or positive sharp waves) or subsequent clinical evidence of persistent muscle wasting that could not be accounted for by disuse alone. Patients were classified as having either acute motor axonal neuropathy or acute motor and sensory axonal neuropathy if there was electromyographic evidence of axonal degeneration together with a reduction of more than 50 percent of the lower limit of the amplitudes of compound muscle action potentials or sensory nerve action potentials of the laboratory concerned in the presence of normal motor conduction velocities, distal motor latencies, and minimum F-wave latencies. Miller Fisher syndrome was diagnosed in patients who presented with the triad of ataxia, ophthalmoplegia, and areflexia in the absence of clinically important limb weakness.<sup>8</sup> Patients who were not studied electrophysiologically or for whom insufficient evidence was available to determine whether demyelination or axonal degeneration was present were considered electrophysiologically unclassifiable, even if the clinical and cerebrospinal fluid findings were consistent with the presence of Guillain-Barré syndrome.

### Microbiologic Investigations

Stool samples were cultured by the transfer of specimens onto selective campylobacter medium (CCDA, Oxoid) with a swab and wire loop. Before being plated, samples were also incubated in Preston enrichment medium for 24 to 48 hours at 37°C to encourage the growth of campylobacters present in numbers too low to be detected by direct inoculation. Specimens were also diluted in nutrient broth No. 2 (Oxoid), centrifuged, and filtered through 65- $\mu$ m filters (Millipore), and the filtrate was spun for five minutes. The sediment was then plated onto Columbia sheep's blood agar plates (Oxoid) and incubated for 24 to 48 hours at 37°C. This filtration method was used to detect campylobacter organisms that may have been sensitive to the antibiotics contained in the CCDA medium. All plates were incubated at 37°C for up to 72 hours and examined daily. Cultures were checked initially with Gram's stain, and the identity of *C. jejuni* colonies was confirmed through tests for oxidase and for the ability to hydrolyze sodium hippurate. All positive cultures were then serotyped according to the Penner system by Dr. Robert Owen at the National Collection for Tissue Cultures, Colindale, United Kingdom.

### Serologic Studies

Serum samples were screened for IgG, IgA, and IgM antibodies against *C. jejuni* by an enzyme-linked immunosorbent assay (ELISA) as described elsewhere,<sup>9</sup> at dilutions of 1:200 and 1:2000. The assay was performed on serum samples from 103 patients, 74 hospital controls, and 75 household controls. All samples had been coded and were assayed blindly in triplicate wells. Reproducibility was monitored with a set of positive and negative control serum samples, and each assay contained both patient and control samples to control for the effects of day-to-day variation. Optical-density values were considered high when they were greater than the mean +2 SD for the hospital-control group for each serum dilution.

### Criteria for *C. jejuni* Positivity

Subjects were considered *C. jejuni*-positive if they had one of the following: a positive stool culture for *C. jejuni*, high optical densities for two or three antibody classes at serum dilutions of both 1:200 and 1:2000 with a negative stool culture, and high optical densities for IgA or IgG at dilutions of 1:200 and 1:2000 and a definite history of a diarrheal illness within the previous 12 weeks but negative stool cultures for *C. jejuni*.

High optical densities for IgM antibodies to *C. jejuni* were found in patients with both salmonella and shigella enteritis, and therefore their presence alone was not regarded as specific for *C. jejuni* infection. Similarly, patients with elevated levels of a single IgG or IgA

antibody class but without a history of recent diarrheal illness were also excluded in order to minimize the number of false positive results.

### Statistical Methods

Differences in proportions were tested by a chi-square test with Yates' correction or Fisher's exact test. Differences in outcome at one year were compared with the use of the chi-square test for trend. All other comparisons between groups were made with either Student's unpaired t-test, if the data variables were normally distributed, or the Mann-Whitney U test if they were not. Logistic-regression models were used to compare the odds ratios for poor prognostic factors. Two-tailed P values have been used throughout.

## RESULTS

### Study Population

We recruited 109 patients with Guillain-Barré syndrome or Miller Fisher syndrome. Six patients were subsequently excluded: three with a relapsing and remitting course in whom chronic inflammatory demyelinating polyradiculoneuropathy was diagnosed, one in whom acute transverse myelitis was diagnosed retrospectively when upper motor neuron signs developed, one in whom paraneoplastic neuronopathy was found post mortem, and one with non-Hodgkin's lymphoma who had weakness complicated by cord compression, vincristine-induced neuropathy, and possible lymphomatous infiltration. Ninety-three hospital controls and 98 household controls were recruited for the remaining 103 patients. Fifteen patients lacked either a hospital control or a household control. Seven patients had been given a clinical diagnosis of Miller Fisher syndrome, and 96 had Guillain-Barré syndrome.

Blood samples were collected from 103 patients (100 percent), 85 household controls (87 percent), and 81 hospital controls (87 percent). Stool specimens were obtained from 100 patients (97 percent), 78 household controls (80 percent), and 62 hospital controls (67 percent). Overall, neither stool nor blood samples were collected for 4 household controls (4 percent) and 10 hospital controls (11 percent).

The mean ( $\pm$ SD) age of the patients was 48 $\pm$ 19 years; of the household controls, 53 $\pm$ 17 years; and of the hospital controls, 48 $\pm$ 17 years. There were no significant differences in age among the three groups or in sex ratio between the patients and the hospital controls (the ratio of men to women was 66:37 among the patients and 52:41 among the hospital controls). The household controls were usually the patients' spouses, and therefore the sex ratio was inverted (39:59).

There was no significant difference in age between the *C. jejuni*-positive (50.1 $\pm$ 17.3 years) and the *C. jejuni*-negative (47.8 $\pm$ 19.9 years) groups. The ratio of men to women, however, was 3.5:1 in the *C. jejuni*-positive group and 1.5:1 in the *C. jejuni*-negative group (P=0.14).

### Frequency of *C. jejuni* Infection in Patients with Guillain-Barré Syndrome and Controls

Twenty-seven patients (26 percent) were found to be *C. jejuni*-positive, as compared with two household controls (2 percent, P<0.001) and one hospital control

(1 percent,  $P < 0.001$ ). Asymptomatic infection occurred in eight patients whose diagnosis was based on serologic analysis and in one control who had three positive stool cultures. Table 1 shows the numbers of subjects in each diagnostic group. The difference in the frequency of *C. jejuni* infection between patients and household controls was still significant according to McNemar's test for matched samples ( $P < 0.001$ ) after the exclusion of unmatched patients, three of whom were positive for *C. jejuni*.

Nineteen of the 27 patients who were positive for *C. jejuni* (70 percent) had a diarrheal illness within the 12 weeks preceding the development of Guillain-Barré syndrome, as compared with 5 of 76 of the *C. jejuni*-negative patients (7 percent,  $P < 0.001$ ). Conversely, a preceding upper respiratory tract infection was more frequent in the *C. jejuni*-negative group (34 of 76, as compared with 3 of 27;  $P = 0.004$ ).

#### Characteristics of *C. jejuni*-Positive Patients with Preceding Diarrheal Illness

Seventeen of 19 patients with a preceding diarrheal illness (89 percent) reported that the diarrhea was watery in nature, and 2 patients (11 percent) reported bloody diarrhea. The duration of the diarrheal illness ranged from 1 day to 8 weeks (median, 6 days), and the median interval between the onset of diarrhea and neuropathic symptoms was 9 days (range, 2 to 20). *C. jejuni* was cultured from eight of the *C. jejuni*-positive patients (30 percent), from whose cultures four isolates were successfully grown in our laboratory. One

Table 2. Characteristics of 19 *C. jejuni*-Positive Patients with Preceding Diarrheal Illness.\*

| TYPE OF DIARRHEA | DURATION (DAYS) | DAYS TO NEUROPATHY | ISOLATION OF <i>C. JEJUNI</i> | PENNER SEROTYPE | DAYS TO STUDY VENESECTION | ANTIBODY RESPONSE |
|------------------|-----------------|--------------------|-------------------------------|-----------------|---------------------------|-------------------|
| Watery           | 6               | 14                 | No                            | —               | 22                        | IgG, IgA, IgM     |
| Bloody           | 24              | 12                 | Yes                           | 64              | 30                        | IgM               |
| Watery           | 5               | 10                 | No                            | —               | 23                        | IgG               |
| Watery           | 12              | 9                  | No                            | —               | 21                        | IgG, IgA, IgM     |
| Watery           | 2               | 2                  | Yes                           | 1               | 23                        | Absent            |
| Watery           | 7               | 8                  | Yes                           | ND              | 26                        | Absent            |
| Watery           | 4               | 4                  | Yes                           | ND              | 62                        | Absent            |
| Watery           | 5               | 5                  | No                            | —               | 12                        | IgG, IgM          |
| Watery           | 6               | 5                  | Yes                           | ND              | 32                        | IgG               |
| Bloody           | 4               | 9                  | No                            | —               | 46                        | IgG, IgA, IgM     |
| Watery           | 14              | 14                 | Yes                           | NT              | 20                        | IgG, IgA, IgM     |
| Watery           | 2               | 6                  | No                            | —               | 15                        | IgG, IgM          |
| Watery           | 6               | 9                  | No                            | —               | 17                        | IgG, IgA, IgM     |
| Watery           | 6               | 10                 | Yes                           | NT              | 25                        | IgG               |
| Watery           | 56              | NK                 | No                            | —               | NK                        | IgA               |
| Watery           | 7               | 9                  | No                            | —               | 30                        | IgG               |
| Watery           | 1               | 20                 | No                            | —               | 62                        | IgG               |
| Watery           | 5               | 9                  | Yes                           | ND              | 36                        | IgG, IgA          |
| Watery           | 4               | 7                  | No                            | —               | 26                        | IgG               |

\*ND denotes not determined, NT not typeable, and NK not known.

was identified as Penner serotype 1, and one as serotype 64; two could not be typed. The other four isolates had been cultured by the local microbiology laboratory before the onset of Guillain-Barré syndrome and discarded, so they were not available for serotyping. Sixteen of the patients with diarrhea (84 percent) had measurable serum antibody responses; five of these (31 percent) had elevated levels of three classes of immunoglobulins, three (19 percent) had elevated levels of two classes, and eight (50 percent) had elevated levels of one class, most commonly IgG alone. Three culture-positive patients (38 percent) did not have an antibody response, even though they were tested at sufficient intervals (median, 26 days; range, 23 to 62) after the initial diarrheal illness for antibodies to have been produced (Table 2).

#### Neurologic Symptoms and Outcomes

Eighteen of the 27 *C. jejuni*-positive patients (67 percent) presented with weakness as their first symptom, as compared with 27 of the 76 *C. jejuni*-negative patients (36 percent,  $P = 0.01$ ). There were no significant differences between the two groups in the proportion of patients presenting with sensory disturbance, pain, or other symptoms (e.g., dysarthria, dysequilibrium, or diplopia). The *C. jejuni*-positive group took significantly longer ( $P = 0.03$ ) to be able to walk unaided (median, 89 days; range, 16 to 386) than the *C. jejuni*-negative group (median, 45 days; range, 8 to 350). There was no difference between groups in the duration of hospitalization. There were no differences between the two groups in the degree of overall disability and arm, facial, and bulbar weakness at the peak of the illness. *C. jejuni*-positive patients, however, had significantly

Table 1. Criteria for the Diagnosis of *C. jejuni* Infection in Patients and Household Controls on the Basis of Microbiologic and Serologic Data.

| CRITERION   | PATIENTS (N = 103)* | HOUSEHOLD CONTROLS (N = 94)† | P VALUE |
|---|---------------------|------------------------------|---------|
|   | number (percent)    |                              |         |
| Positive stool culture  | 8 (8)               | 1 (1)                        | 0.04    |
| Elevated immunoglobulin levels, negative stool culture                  | 14 (14)             | 0                            | <0.001  |
| History of diarrhea, elevated IgA or IgG levels, negative stool culture | 5 (5)               | 1 (1)                        | 0.21    |
| Total   | 27 (26)             | 2 (2)                        | <0.001  |

\*Percentages do not add up to total because of rounding.

†Four of the 98 household controls had neither blood nor stool samples collected.

Table 3. Outcomes at One Year.\*

| OUTCOME   | C. JEJUNI-<br>POSITIVE<br>(N = 26) | C. JEJUNI-<br>NEGATIVE<br>(N = 75)† | ODDS<br>RATIO |
|---|------------------------------------|-------------------------------------|---------------|
|   | number (percent)                   |                                     |               |
| Not disabled or slightly disabled (disability grades 0 and 1) | 9 (35)                             | 51 (68)                             | 1.0           |
| Moderately disabled (disability grade 2)                      | 11 (42)                            | 17 (23)                             | 3.7           |
| Severely disabled (disability grades 3, 4, and 5)             | 5 (19)                             | 2 (3)                               | 14.2          |
| Death (disability grade 6)                                    | 1 (4)                              | 5 (7)                               | 1.1           |

\*Chi-square value for linear trend is 5.1 (P=0.02).

†Percentages do not add up to 100 because of rounding.

less severe sensory symptoms (mean sensory grade, 1.4, vs. 2.0 for the *C. jejuni*-negative group; P=0.03).

After one year, two patients (one from each group) had been lost to follow-up. Analysis of outcomes revealed a significantly greater disability at one year in the *C. jejuni*-positive group (P=0.02) (Table 3).

#### Electrophysiologic Diagnoses of Patients with Guillain-Barré Syndrome

When patients who could not be classified electrophysiologically and those with Miller Fisher syndrome were excluded, acute motor or motor and sensory axonal neuropathy occurred more frequently in the *C. jejuni*-positive group than in the *C. jejuni*-negative group (P=0.002). Conversely, patients who were positive for *C. jejuni* were less likely to have acute inflammatory demyelinating polyradiculoneuropathy (P=0.003). Patients with acute inflammatory demyelinating polyradiculoneuropathy who were positive for *C. jejuni* were twice as likely as patients who were negative for *C. jejuni* to have axonal degeneration as well, although this was only significant at the 10 percent level (P=0.08). The proportions of patients with Miller Fisher syndrome were similar in both groups (Table 4).

#### Analysis of Poor Prognostic Factors

Six patients died by the end of one year, and seven were severely disabled (one was receiving assisted ventilation, one was confined to bed, and five were unable to walk 5 m without aid). These patients were classified as having poor outcomes. Their characteristics at presentation were compared with those of the good-outcome group, which consisted of the remaining 88 patients (2 were lost to follow-up) who had recovered to the level of disability grade 2 or better at the end of one year. Multivariate analysis revealed significant effects of increasing age, *C. jejuni* positivity, the need for ventilatory support, and becoming confined to bed within two days of the onset of neuropathic symptoms (Table 5).

#### DISCUSSION

This study aimed specifically to determine the frequency and clinical features of antecedent *C. jejuni* in-

fection in a large cohort of patients with Guillain-Barré syndrome or Miller Fisher syndrome. We found that 26 percent of the patients with Guillain-Barré syndrome had evidence of *C. jejuni* infection. This is higher than the 14 percent reported by Winer et al.<sup>10</sup> in a comparable study of 99 patients with Guillain-Barré syndrome carried out in 1983–1984. The diagnosis of *C. jejuni* infection in that study, however, was made only by complement-fixation tests (which measure predominantly IgM antibodies), without stool cultures, and therefore probably underestimated the true frequency. Seven of our patients had no IgM antibodies. Kuroki et al.<sup>11</sup> in Japan studied 46 patients, of whom 30 percent had stool cultures positive for *C. jejuni*, and an additional 11 percent had serologic evidence of infection. This was not a case-control study, and therefore the higher frequency of *C. jejuni* infection in Japanese patients with Guillain-Barré syndrome may have represented an underlying high frequency in the general population of that region.

Two retrospective serologic studies of Guillain-Barré syndrome that used an ELISA to detect antibodies against *C. jejuni* infection found seropositivity rates of 36 percent<sup>12</sup> and 38 percent.<sup>3</sup> They may have been biased in favor of more severely affected patients and hence reported a higher frequency of *C. jejuni*-positive cases. The patients in the study by Mishu et al.<sup>12</sup> were drawn from three university medical centers that accepted tertiary referrals, and those in the study by Kaldor and Speed<sup>3</sup> were drawn from an infectious-diseases institution. Thirty-three of 56 patients (59 percent) in the latter study required ventilatory support — a frequency that is double that reported in the literature. To avoid possible selection bias, we included all the patients from both district general hospitals and teaching hospitals. Our study therefore included patients with a wider spectrum of diseases, without so much bias toward either severe Guillain-Barré syndrome or a recent diarrheal illness.

Our criteria for the diagnosis of *C. jejuni* positivity

Table 4. Electrophysiologic Diagnoses of Patients with Guillain-Barré Syndrome.\*

| DIAGNOSIS†   | C. JEJUNI-<br>POSITIVE<br>(N = 25) | C. JEJUNI-<br>NEGATIVE<br>(N = 62) | P VALUE |
|--|------------------------------------|------------------------------------|---------|
|  | number (percent)                   |                                    |         |
| AIDP only  | 10 (40)                            | 47 (76)                            | 0.003   |
| AIDP and AD‡                                       | 9 (36)                             | 14 (23)                            | 0.31    |
| Acute motor or motor and sensory axonal neuropathy | 6 (24)                             | 1 (2)                              | 0.002   |
| Unclassified                                       | 0                                  | 9 (11)                             | 0.1     |

\*Seven patients were excluded because they had Miller Fisher syndrome: two in the *C. jejuni*-positive group (8 percent) and five in the *C. jejuni*-negative group (6 percent) (P=1.0).

†AIDP denotes acute inflammatory demyelinating polyradiculoneuropathy, and AD axonal degeneration.

‡In the *C. jejuni*-positive group, 47 percent of all the patients with acute inflammatory demyelinating polyradiculoneuropathy also had axonal degeneration; in the *C. jejuni*-negative group, 23 percent had both conditions (P=0.08).

Table 5. Multivariate Analysis of Factors Contributing to a Poor Outcome after One Year.\*

| FACTOR                           | GOOD OUTCOME     | POOR OUTCOME | P VALUE | ODDS RATIO (95% CI) |
|----------------------------------|------------------|--------------|---------|---------------------|
|                                  | number (percent) |              |         |                     |
| Age                              | NA               | NA           | <0.01   | 3.0† (1.4–6.1)      |
| <i>C. jejuni</i> positivity      |                  |              |         |                     |
| Yes                              | 20 (23)          | 6 (46)       |         |                     |
| No                               | 68 (77)          | 7 (54)       | 0.03    | 7.3 (1.2–45.1)      |
| Ventilatory support              |                  |              |         |                     |
| Yes                              | 19 (22)          | 7 (54)       |         |                     |
| No                               | 69 (78)          | 6 (46)       | <0.01   | 15.9 (2.4–106.7)    |
| Confinement to bed within 2 days |                  |              |         |                     |
| Yes                              | 20 (23)          | 9 (69)       |         |                     |
| No                               | 68 (77)          | 4 (31)       | 0.01    | 8.6 (1.7–43.7)      |

\*NA denotes not applicable as a continuous variable, and CI confidence interval.

†Odds ratio is for age intervals of 10 years.

were made particularly stringent to exclude any false positive serologic results. We have found that an isolated IgM response to *C. jejuni* may also occur after salmonella enteritis. In addition, patients with elevated levels of a single class of antibody but no diarrhea were excluded, since it has been shown previously that some people, such as those who regularly drink raw milk, have elevated levels of IgG antibodies.<sup>13</sup> Conversely, not all infected patients have a measurable antibody response. It is probable, therefore, that one or more of the five patients who had an antecedent diarrheal illness but who were classified as *C. jejuni*-negative had been infected with the organism. The true frequency of antecedent *C. jejuni* infection is probably higher than 26 percent, making *C. jejuni* the most common single identifiable pathogen in Guillain-Barré syndrome.

Guillain-Barré syndrome was more likely to develop in men after *C. jejuni* infection than in women, which either suggests a sex-linked predisposition or results from a preponderance of male patients among those with *C. jejuni* infection. Men are more commonly infected by *C. jejuni*,<sup>14</sup> and this may explain the male predominance seen in our study and also reported by Mishu et al.<sup>12</sup> Our analysis of the characteristics of the diarrheal illnesses does not suggest any unusual features specific to *C. jejuni* strains that cause Guillain-Barré syndrome, except perhaps that watery rather than bloody diarrhea predominates. In addition, we could not confirm previous studies from Japan that suggest a predominance of the Penner 19 serotype.<sup>11</sup>

The median interval from the onset of diarrhea to the onset of neuropathic symptoms for all *C. jejuni*-positive patients was nine days, suggesting that Guillain-Barré syndrome occurs as a consequence of an immune response to *C. jejuni* rather than as a direct effect of the organism or one of its toxins. The nature of the immune response is not yet known, although immunologic cross-reactivity between *C. jejuni* lipopolysaccharide antigens and ganglioside GM<sub>1</sub>, a minor axolemmal glycolipid, has been described by Yuki et al.<sup>15</sup> The spectrum of *C. jejuni*-induced Guillain-Barré syndrome

ranges from mild cases of demyelinating neuropathy to a rapidly progressive axonal neuropathy with prolonged recovery and severe residual disability. Two of our patients with *C. jejuni* infection had Miller Fisher syndrome, and both recovered well, as have other patients described in the literature.<sup>4,16</sup>

The patients in the *C. jejuni*-positive group as a whole were significantly more likely to present with a purely motor syndrome defined by the absence of sensory symptoms and signs. Although there was no significant difference in the degree of overall disability at the peak of the illness, *C. jejuni*-positive patients took longer to recover and were more likely to be severely disabled at the end of one year. In addition, being *C. jejuni*-positive was significantly associated with a poor outcome after correction for other poor prognostic factors. This finding correlates with the significantly greater proportion of *C. jejuni*-positive patients who had electrophysiologic and clinical evidence of axonal degeneration, either as a primary axonopathy or in association with acute inflammatory demyelinating polyradiculoneuropathy. Within the overall spectrum of Guillain-Barré syndrome, there is a subgroup of patients presenting with a “hyperacute” onset, commonly after having gastroenteritis, that is characterized by rapid progression, slow recovery, and substantial residual disability. The results of our study suggest that many of these patients have had *C. jejuni* infection and are similar to the patients described by Palace and Hughes.<sup>17</sup>

Some investigators dispute the evidence of primary axonal degeneration in Guillain-Barré syndrome,<sup>18</sup> but support for this entity comes from the electrophysiologic and histologic findings of a seasonal form of acute motor axonal neuropathy in rural areas of northern China.<sup>19</sup> The majority of Chinese patients presenting with acute areflexic paralysis in the summer months met electrodiagnostic criteria for a purely motor axonopathy but made a good recovery nevertheless. Furthermore, a high percentage of affected children had IgG and IgM antibodies against *C. jejuni* as compared with hospital controls. This suggests that *C. jejuni* infection may be responsible for a large proportion of patients presenting with predominantly motor axonal neuropathy.

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