Association between *Campylobacter* Infection and Guillain-Barré Syndrome

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Guillain-Barré syndrome (GBS), a neurologic disease that produces ascending paralysis, affects people all over the world. Acute infectious illnesses precede 50%–75% of the GBS cases. Although many infectious agents have been associated with GBS, the strongest documented association is with *Campylobacter* infection. The first line of evidence supporting *Campylobacter* infection as a trigger of GBS is anecdotal reports. The second line of evidence is serologic surveys, which have demonstrated that sera from GBS patients contain anti–*Campylobacter jejuni* antibodies, consistent with recent infection. Finally, culture studies have proven that a high proportion of GBS patients have *C. jejuni* in their stools at the time of onset of neurologic symptoms. Neurologic symptoms are more severe and more likely to be irreversible when GBS is preceded by *C. jejuni* infection. One of every 1058 *Campylobacter* infections results in GBS, and 1 of 158 *Campylobacter* type O:19 infections results in GBS.

Guillain-Barré syndrome (GBS) is a neurologic disease characterized by ascending paralysis that can lead to respiratory muscle compromise and death. GBS is the most common cause of acute neuromuscular paralysis in the developed world. Considerable evidence suggests that GBS is a postinfectious phenomenon. Herein, I will review the data showing that *C. jejuni* infection is associated with GBS, explore the differences between GBS induced by *Campylobacter jejuni* and GBS induced by other causes, and assess the risk of developing GBS after infection with *Campylobacter* organisms.

GBS and Preceding Infection

It has long been recognized that frequently GBS is preceded by an acute infectious illness. In 1892, Sir William Osler, a renowned late nineteenth and early twentieth century physician, called the syndrome ''acute postinfectious polyneuritis'' [1]. Investigators all over the world have confirmed that in 50%–75% of the cases, GBS is preceded by a recognized acute infectious illness (table 1). Upper respiratory infections are frequently described antecedent events, and gastrointestinal infections, including diarrheal illness, precede GBS in 10%–30% of the cases [2].

Pathogens associated with onset of GBS include *Mycoplasma pneumoniae,* hepatitis B virus, cytomegalovirus, vari-

cella-zoster virus, Epstein-Barr virus, rubeola, and human immunodeficiency virus [3–7]. Most of these associations were based upon anecdotal reports or uncontrolled surveys. *Campylobacter* species were not reported in association with GBS until 1982 [8] because until recent years, culturing of stools for this species was not routinely done, even in patients with diarrhea. Therefore, earlier cases of *Campylobacter*-associated GBS may have been unrecognized.

Association of *C. jejuni* Infection with GBS

The evidence that *C. jejuni* is the most important trigger of GBS comes from 3 sources—anecdotal reports, serologic studies, and culture data. As with many new medical discoveries, the association between GBS and *C. jejuni* was first described in clinical anecdotes. In 1982, Rhodes and Tattersfield [8] were the first to report on a patient who developed GBS 10 days after *C. jejuni* infection. Almost immediately, there was a flurry of responses from other physicians who had also seen cases of GBS that were preceded by *C. jejuni* infection [9–13]. In these early reports, it was frequently noted that GBS following *C. jejuni* infection was severe, with extensive axonal damage. These reports also described the temporal relationship between *C. jejuni* infection and GBS; neurologic symptoms typically occur 10 days to 3 weeks after onset of diarrhea. The longest reported interval between onset of *C. jejuni* enteritis and onset of GBS symptoms is 23 days [11].

The mean excretion time of *C. jejuni* in stools is only 16 days [14], whereas antibodies to *C. jejuni* may remain elevated for several weeks after acute infection [15]; therefore, serologic assays have been done to assess the frequency of preceding *C. jejuni* infection in GBS patients. Several studies have documented a high prevalence of antibodies to *C. jejuni* in the serum of patients with GBS [16–21]. Using immunodot assays to determine the frequency of *C. jejuni* antibodies, Gruenwald et al. [18] found that 3 (18%) of 17 patients with GBS had ele-

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Table 1. Frequency of antecedent infections among patients with Guillain-Barré syndrome (GBS).

Location	Year of study	No. with GBS	% with recognized antecedent infectious illness
Great Britain	1964	52	69
Europe, United States	1966	1100	58
Minnesota	1978	40	70
Norway	1985	109	57
England	1988	100	55
India	1988	56	32
France	1989	71	50
Spain	1990	15	53
Indonesia	1990	28	75

vated titers in two or more immunoglobulin classes. However, the absence of a control group in this investigation makes it difficult to interpret the results. Similarly, using a complement fixation technique, Winer et al. [17] found that 14 (14%) of 99 patients with GBS had positive *C. jejuni* serologic tests, compared with only 2% of controls. They also looked for but did not find evidence of preceding infection with parvovirus, Epstein-Barr virus, and *M. pneumoniae.* However, serum specimens from their patients could have been obtained up to 2 months after onset of neurologic symptoms, substantially reducing the sensitivity of any serologic test. Kaldor and Speed [19] used nonstandardized methods to study serum from 56 patients with GBS and from 57 controls; in their unblinded analysis, they found that 38% of the patients and none of the controls met their criteria for positive serologic responses. Serologic tests were done as a part of a Japanese study of GBS patients; 36% were seropositive [20].

In a large, blinded, case-control study of 118 GBS patients and 113 controls in the United States, GBS patients were more than five times as likely to have serologic evidence of a recent *Campylobacter* infection [22]. The association was detected using all three immunoglobulin classes, and it was observed in all age groups and in all seasons. However, it was most pronounced in those >60 years old and during summer months. In this study, male patients also were more likely than female GBS patients to have evidence of preceding *C. jejuni* infection.

C. jejuni antibodies also were found in the serum of patients with acute motor axonal neuropathy (AMAN), an illness that is similar to GBS [23]. Outbreaks of AMAN occur in northern China each summer and fall; most patients are children living in rural areas. In the summer and fall of 1992, investigators obtained serum from 38 children in northern China who were diagnosed with GBS; all samples were obtained within 30 days of onset of neurologic symptoms. Sera also were obtained from 82 controls of similar age and sex. Forty-one controls lived in the one village and 41 in neighboring villages. Sera from patients and controls were assayed blindly. Nine patients (24%) were seropositive, compared with only 3 controls (4%). Comparing patients with all 82 controls, patients were more than eight times as likely to have a positive serologic response. Electrophysiologic studies of these 38 patients showed that 21 had AMAN, 12 had GBS, 5 were either inexcitable or equivocal. These results suggest *C. jejuni* infection may play a role in the pathogenesis of GBS and of AMAN.

Although the results of these serologic assays support the hypothesis that *C. jejuni* infection may be a common trigger in the initiation of GBS, the reference standard for determining if a person is infected with *C. jejuni* infection is not a serologic test but culture of the organism. Skeptics could claim that GBS patients form antibodies to a variety of autoantigens and that the serologic studies are measuring this nonspecific elevation in antibody titers rather than true infection. However, obtaining culture confirmation of an association with GBS and preceding *C. jejuni* infection is difficult because most patients with *Campylobacter* infection would have already cleared their stools by the time their GBS symptoms began. Nevertheless, several investigators have succeeded in isolating *C. jejuni* from the stools of patients with GBS at the onset of their neurologic symptoms (table 2). *Campylobacter* is not a part of normal stool flora, and detection of the organism would not be expected in the absence of recent infection. Thus, the serologic and cultural studies demonstrate that at least 30%–40% of GBS patients have been infected with *Campylobacter* in the 10 days to 2 weeks prior to the onset of their neurologic symptoms. Because of the lag time between *C. jejuni* infection and onset of neurologic symptoms, these numbers likely underestimate the association between *C. jejuni* infection and GBS.

Disease Severity in *C. jejuni*–Associated GBS

Even more interesting is the observation that when GBS occurs after *Campylobacter* infection, it may be more severe and result in more irreversible neurologic damage than GBS associated with other triggers. Initially this was noted in anecdotal reports by some researchers but not by others. Three recent studies, however, have lent credence to this hypothesis.

Table 2. Stool cultures for *Campylobacter jejuni* in patients with Guillain-Barré syndrome.

Investigator [reference]	Country	Year	No. of patients with culture	% with *C. jejuni*
Speed [12]	Australia	1987	4	25
Ropper [16]	United States	1988	9	44
Gruenwald [18]	United States	1991	4	50
Kuroki [21]	Japan	1993	46	30
Rees [24]	England	1995	100	8
Enders [25]	Germany	1994	26	15
Hariharan [26]	India	1996	8	38

Campylobacter Infection and GBS

Of 58 GBS patients studied by Vriesendorp and colleagues [27], 10 were *C. jejuni*–positive, and of these, 3 had severe disease. ''Severe disease'' was defined as fulminating disease with quadriplegia and ventilatory dependence within 24–48 h of onset. None of the 48 patients without *C. jejuni* infection had severe disease. In a British study of 101 GBS patients, 23% of the patients with *Campylobacter* infection were unable to walk unassisted 1 year after the onset of symptoms, compared with only 9% of *Campylobacter*-negative GBS patients [24]. Similarly, in The Netherlands, 14 of 24 *C. jejuni*–infected GBS patients treated with plasma exchange were unable to walk unassisted 6 months after the onset of their symptoms, compared with only 12% of similarly treated GBS patients without evidence of preceding *Campylobacter* infection [28]. Because many of these patients' infections were documented by culture, it is unlikely that elevated nonspecific antibody titers in GBS patients were a confounding factor for poor prognosis.

Risk of Developing GBS after *C. jejuni* Infection

Although *C. jejuni* infections are a common trigger of GBS, they occur far more commonly than GBS; therefore the risk of developing GBS after infection with *Campylobacter* is actually quite low. The US Centers for Disease Control and Prevention estimates that there are 1000 cases of *C. jejuni* infection per 100,000 population per year [29]. The National Center for Health Statistics Hospital Discharge data documented 7874 cases in the United States in 1995. Therefore, assuming that 30% of GBS cases are preceded by *C. jejuni* infection and that the US population is 250 million, we can estimate that 1 of every 1058 cases of *C. jejuni* infection is followed by GBS.

The risk of developing GBS may be higher after infection with *C. jejuni* type O:19. Of 12 *C. jejuni* isolates from Japanese GBS patients, 10 were of serotype 19 [21]. This serotype 19 represents <2% of *C. jejuni* isolates from patients with uncomplicated enteritis in Japan. The association between Penner O19 and GBS is not as strong outside of Japan. For example, in the United States, 2 of 7 GBS-associated *Campylobacter* isolates were Penner type O:19 [30]; this is still significant because Penner type O:19 accounts for only 3% of isolates from patients with uncomplicated enteritis. In a British study [24], 4 *Campylobacter* isolates from GBS patients were serotyped; 2 were nontypeable, and the other 2 were not type O:19. If it is assumed that 20% of GBS-associated *C. jejuni* isolates are serotype O:19, then the risk of developing GBS after infection with *C. jejuni* type O:19 is 1 in 158.

Conclusions

In summary, at least 30%–40% of GBS patients have had a preceding *Campylobacter* infection. The timing of GBS following *C. jejuni* infection (1–3 weeks) suggests a humoral immunopathogenic mechanism. One of every 1058 *Campylobacter* infections results in GBS, and 1 of 158 *Campylobacter* type O:19 infections results in GBS. *Campylobacter*-associated GBS is more severe and results in more irreversible neurologic damage.

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