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Role of Infection Due to *Campylobacter jejuni* in the Initiation of Guillain-Barré Syndrome

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Recent reports suggest that infection with *Campylobacter jejuni*, a common enteric pathogen, may cause Guillain-Barré syndrome (GBS) by triggering demyelination of peripheral nerves. GBS is preceded by an acute infectious illness (due to a variety of agents) in 50%–75% of cases; the onset of neurological symptoms is preceded by diarrhea in 10%–30% of cases. In the last decade, more than 20 published anecdotal reports and case series have described patients with *C. jejuni* infection documented 1–3 weeks before onset of GBS. Cultures of fecal samples obtained at the onset of neurological symptoms from patients with GBS have yielded *C. jejuni* in more than 25% of cases. A relatively rare serotype, Penner type O19, is overrepresented among isolates of *C. jejuni* from Japanese patients with GBS. Serological studies suggest that 20%–40% of patients with GBS have evidence of recent *C. jejuni* infection. In summary, infection with *C. jejuni* is a common antecedent to GBS and probably plays a role in initiating demyelination; although several pathogenic mechanisms are possible, none has been proven.

Guillain-Barré syndrome (GBS) is the most common cause of acute neuromuscular paralysis in both adults and children [1, 2]. The annual incidence in the developed world is between 1 and 2 cases per 100,000 population [3, 4]. In recent years infection with *Campylobacter jejuni* has been identified as a potentially important precipitating factor for GBS. *C. jejuni* is the most frequently identified bacterial cause of gastroenteritis in the United States and in other industrialized countries [5]. Most infections with *C. jejuni* produce an acute self-limited diarrheal illness [6]. Although extraintestinal complications of *C. jejuni* infection [7] suggest the involvement of immunopathogenic mechanisms, GBS associated with *C. jejuni* infection has not been well recognized. We review the existing evidence that infection due to *C. jejuni* plays a role in the pathogenesis of GBS, and we discuss possible mechanisms for this association.

GBS as a Postinfectious Syndrome

Guillain-Barré syndrome, sometimes called acute postinfectious polyneuritis, often develops 1–3 weeks after an acute infection of the respiratory or gastrointestinal tract. Osler first noted the association between acute infectious illness and limb weakness and paralysis in 1892 [8]. Epidemiological studies throughout the world have confirmed the association between GBS and preceding infectious illness [3, 9–16]: 50%–75% of patients have such an illness in the weeks preceding onset of GBS (table 1). Specific infectious agents associated with GBS include *Mycoplasma pneumoniae*, hepatitis B virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, rubeola virus, and (most recently) human immunodeficiency virus [17–21]. Although infections of the upper respiratory tract are also frequently described as antecedent events, gastrointestinal infections including diarrheal illness precede GBS in 10%–30% of cases [3, 12, 16].

Association of *C. jejuni* with GBS

In 1977, Skirrow reported that *C. jejuni* was a common cause of acute diarrheal illness in England and established methods that facilitated isolation of this organism [22]. Gradually, this advance was incorporated into the routines of many clinical microbiology laboratories. However, even at present, many laboratories attempt isolation of *C. jejuni* from fecal specimens only upon special request if at all, and few laboratories utilize appropriate techniques for isolation of all members of the rapidly expanding genus *Campylobacter* (and now *Arcobacter*). Thus, any estimate of the role of these organisms in the causation of human illness is likely to be low.

In 1982, Rhodes and Tattersfield reported a case of GBS following enteric infection with *C. jejuni* [23]. Because routine culture of stool specimens for campylobacters was so new, the authors suggested that previous cases of *Campylobacter*-associated GBS may have gone unrecognized. Since then, there have been 21 more reports of individual patients

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

Location of study [reference]	Year	No. of patients with GBS	Percentage with recognized antecedent infectious illness
Great Britain [10]	1964	52	69
Europe, United States [9]	1966	1,100	58
Minnesota [3]	1978	40	70
Norway [11]	1985	109	57
England [12]	1988	100	55
India [13]	1988	56	32
France [14]	1989	71	50
Spain [15]	1990	15	53
Indonesia [16]	1990	28	75

and series of patients with GBS preceded by *C. jejuni* infection [12, 24–44]; data from reports that described patient characteristics are summarized in table 2. Although almost three times as many cases of *C. jejuni*–associated GBS have been reported among male patients as among female patients, it is uncertain whether this difference reflects demographic reality or a selection bias in the reporting of cases. Initial reports indicated that patients with *C. jejuni*–associated GBS had severe disease, with extensive axonal damage and prolonged debilitation [23–25]. Subsequent reports, however, have also described milder cases of GBS occurring in association with *C. jejuni* infection [26, 27].

After the first anecdotal reports, some investigators began to routinely culture the stools of patients with GBS for *C. jejuni*. However, because the duration of convalescent excretion of *C. jejuni* is brief (mean, 16 days from onset of diarrheal symptoms) [45] and because neurological symptoms in *C. jejuni*–associated GBS usually develop 1–3 weeks after the onset of diarrhea [23–26], cultures of fecal samples obtained at the onset of neurological symptoms may yield "false" negative results that are misleading. Despite this limitation, Speed et al. isolated *C. jejuni* from stool cultures of one of four patients with GBS [40]. Ropper found that 13 (12%) of 106 patients with GBS had diarrhea in the 10 days preceding the onset of neurological symptoms; stool was cultured in nine of these cases, and *C. jejuni* was isolated in four instances (44%) [31]. Kuroki et al. isolated *C. jejuni* from seven (88%) of eight pediatric patients with GBS in Japan [32]. Because the patients were not related to one another and became ill in different years, it is not likely that these strains represented a common-source outbreak. Four of these strains were of Penner type O19; the remaining three isolates were not available. Other Japanese investigators serotyped four additional isolates of *C. jejuni* from patients with GBS and found that these four strains were also of Penner type O19 [33]. Since Penner type O19 accounts for fewer than 2% of *C. jejuni* strains in Japan [46], these studies suggest that an uncommon serotype of *C. jejuni* may be overrepresented among strains associated with GBS.

Despite the brief duration of convalescent excretion of *C. jejuni*, serological tests may provide evidence of recent infection even after the bacteria can no longer be isolated from stools. In both natural and experimental infections due to *C. jejuni*, specific IgM and IgG antibody responses peak at 2 weeks, but titers may remain elevated for 4–6 weeks; levels of IgA antibodies also peak at 2 weeks but fall to baseline values within 4 weeks [47]. Thus it may be possible to determine serologically whether GBS patients have had antecedent *C. jejuni* infection. Indeed, several investigators have documented high levels of antibodies to *C. jejuni* in patients with GBS or GBS-like illnesses [12, 28–30]. Although the antibodies were assayed by a variety of techniques, most methods found serological evidence of preceding *C. jejuni* infection in 14%–40% of patients with GBS (table 3).

Taken together, the anecdotal reports, the studies of series of GBS patients whose stools were cultured, and the serological investigations suggest that *C. jejuni* infection may commonly precede GBS. Nevertheless, GBS is a relatively rare disease and is probably an uncommon manifestation of this very frequent bacterial infection. The Centers for Disease Control and Prevention estimates an annual incidence of ~1,000 symptomatic infections with *C. jejuni* per 100,000 population—roughly 2 million cases—in the United States [48]. The annual incidence of GBS in this country has been estimated at 1.7/100,000 population [3], or 4,250 cases. If *C. jejuni* infection is an important antecedent event in only 10%–30% of GBS cases (the minimal estimate based upon serological surveys), then between 425 and 1,275 cases of GBS preceded by *C. jejuni* infection occur in the United States each year (table 4). Therefore, on the basis of the estimated number of cases of GBS preceded by *C. jejuni* infection and the total number of *C. jejuni* infections, it can be calculated that one in every 2,000–5,000 cases of *C. jejuni* infection is followed by GBS. These numbers illustrate that a common problem (*C. jejuni* infection) with an uncommon manifestation (GBS) may represent a common cause of an uncommon disease.

Potential Mechanisms Involved in GBS Following Infection Due to *C. jejuni*

The hallmark of GBS is segmental demyelination of peripheral nerves, with mononuclear infiltrates and edema. Myelin destruction may be mediated by a direct toxic effect or by an immunopathogenic mechanism; in the latter case, either humoral or cellular immune mechanisms could be operative.

Because of the extensive axonal damage noted in the earli-

Table 2. Cases of Guillain-Barré syndrome (GBS) following infection with *C. jejuni*, as described in published reports.

Location, year of study [reference]: patient's age (y)/sex	Days from onset of diarrhea to GBS	Outcome
England, 1982 [23]: 45/M	15	Wheelchair-bound at 8 mo
Finland, 1982 [24]: 42/M	9	Severe deficits at 6 mo
England, 1983 [25]: 34/F	10	Intubated; severe deficits at 6 mo
Australia, 1984 [26]		
34/M	23	Complete recovery at 3 mo
22/F	21	Mild 6th-nerve palsy at 3 mo
England, 1984 [27]: 16/M	10	Complete recovery at 6 mo
England, 1985 [41]: 27/M	7	Complete recovery with minor deficits
Australia, 1986 [37]: 2/F	9	Intubated; hospitalized at 4 mo; complete recovery at 6 mo
New York, 1987 [38]: 69/M	13	Wheelchair-bound at 10 w
Switzerland, 1988 [43]: 19/M	13	Complete recovery at 3 mo
Boston, 1988 [31]		
63/F	7	Wheelchair-bound at 6 mo
74/F	11	Complete recovery at 6 mo
32/M	7	Complete recovery at 6 mo
19/M	10	Complete recovery at 2 mo
Switzerland, 1988 [39]		
38/M	6	Slow recovery over 1 y
81/M	1	Complete recovery at 9 mo
60/M	12	Complete recovery at 1 y
France, 1989 [42]*		
30/M	10	Complete recovery at 28 mo
62/M	8	Complete recovery at 3 mo
74/M	4	Not described
Japan, 1990 [35]*		
25/M	14	Canes required for walking at 6 mo
83/F	7	Bedridden at 3 y
Japan, 1991 [32]		
7/M	?	Complete recovery with minor deficits
9/M	6	Complete recovery with minor deficits
10/F	15	Complete recovery
11/M	5	Complete recovery with minor deficits
13/M	6	Complete recovery
14/M	6	Complete recovery
14/M	7	Improving at 1 mo

* Diagnosis of campylobacter infection made by serological tests; diagnoses in all other reports were culture proven.

est cases, direct toxic damage to neural structures—perhaps attributable to a yet-unrecognized neurotoxin—has been suggested [24]. However, the toxic activity of *C. jejuni* in vitro [49] has not been demonstrated in vivo [50]. The timing of the onset of GBS (1–3 weeks after the peak of the diarrheal illness) also argues against a direct toxic effect of *C. jejuni*.

Two distinct possibilities for mechanisms of immunologic injury have been proposed. (1) Demyelination may result from a specific genetic predisposition. A Japanese investigation showed that all of six patients with GBS who had antecedent infection due to *C. jejuni* possessed the HLA-B35 antigen, whereas only 14% of 3,090 healthy Japanese controls had this antigen [36]. Previous studies of GBS patients had not shown an association with a particular HLA type [51]. (2) Perhaps only a few *C. jejuni* strains are capable of triggering immunologically mediated myelin destruction. The association of Penner serotype O19 with the initiation of GBS [32, 33] suggests that these strains may represent a particularly virulent clone or that the O19 polysaccharide may be either a virulence determinant per se or a marker for other virulence factors.

The neurological target for immunologic injury also is unknown. Serum from a patient with *C. jejuni*–associated GBS reacted strongly with P0, a peripheral nerve myelin–specific protein [34]; this observation suggested that *C. jejuni* pos-

sesses antigens stimulating the production of antibodies that react with peripheral nerve myelin and cause GBS. Similarly, gangliosides found in myelin may be the ultimate target of antibodies formed in response to *C. jejuni* infection; GBS has followed the administration of parenteral gangliosides [52, 53].

GBS following *C. jejuni* infection often is associated with extensive axonal damage, a relatively severe clinical course, and a poor recovery [29]. In one study the documentation of high levels of IgG antibodies recognizing GM1 in two patients with *C. jejuni*–associated GBS and extensive axonal damage suggested the involvement of increased levels of these antibodies in pathogenesis [35]. In another investigation IgA antibodies to GM1 were detected in 15 (28%) of 53 patients with GBS and in only 1 (4%) of 26 controls; the GBS patients with antibodies to GM1 had more extensive axonal involvement and more severe clinical courses [54]. Koski et al. found that titers of IgM antibodies to a neutral glycolipid in peripheral nerve myelin were elevated in all of 12 patients with GBS but in none of 36 controls; the antibodies cross-reacted with Forssman antigen as well as with eukaryotic cell membranes [55]. However, earlier studies by Ilyas et al. showed no increase in levels of antibodies to GM1 in association with GBS [56]. Furthermore, Yuki and colleagues reported that antibodies to GM1 were elevated in patients with severe axonal GBS and no evidence of preceding *C. jejuni* infection [57]. In another investigation of 100 patients with GBS, only 7 had antibodies to peripheral nerve myelin and none had antibodies to galactocerebroside; however, serum samples were collected up to 8 weeks after onset of neurological symptoms [58].

The exact contribution of these factors to the pathogenesis of *C. jejuni*–associated GBS has not been determined. Nevertheless, clinical reports, serological surveys, and isolations of *C. jejuni* from series of patients have made it clear that a substantial proportion of cases of GBS are preceded by *C. jejuni* infection, and it is likely that this infection plays a role in the initiation of demyelination. Toward the goals of better defining this conjunction and developing specific therapies, routine cultures of stool for *Campylobacter* species should become part of the initial evaluation of patients with suspected GBS. Further studies must elucidate the role of *C. jejuni* in initiating GBS and illuminate the mechanisms involved in pathogenesis.

Table 3. Serological evidence of infection due to *C. jejuni* among patients with Gulillain-Barré syndrome (GBS) or GBS-like illness.

Location of study [reference]	No. of patients with GBS	Percentage with positive serological test	Assay
United States [28]	17	18	Immunodot
England [12]	99	14	Complement fixation
Australia [29]	56	38	ELISA
China [30]	32	41	ELISA
United States [44]	118	36	ELISA

Table 4. Estimated annual incidences of infection due to *C. jejuni*, Guillain-Barré syndrome (GBS), and GBS preceded by *C. jejuni* infection in the United States.

Disease	Annual incidence (cases/100,000 population) [reference]	Total cases/y*
C. jejuni infection	1,000 [48]	2,500,000
GBS		
All cases	1.7 [3]	4,250
Cases preceded by *C. jejuni* infection†	0.17–0.51	425–1,275

* Based on estimated U.S. population of 250 million.
† Estimated at 10%–30% of all GBS cases.

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