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Campylobacter jejuni from Patients with Guillain-Barré Syndrome Preferentially Expresses a GD_{1a}-Like Epitope

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GM_1- and GD_{1a}-like ganglioside mimicry in *Campylobacter jejuni* lipooligosaccharide (LOS) is considered to be involved in the pathogenesis of *Campylobacter*-induced Guillain-Barré syndrome (GBS). Compared with gastroenteritis-related isolates, GBS-related *C. jejuni* isolates were strongly associated with the expression of GD_{1a}-like mimicry. The presence of a few genes involved in LOS ganglioside mimicry, *cst-II*, *cgtA*, and *cgtB*, was also associated with GBS-related strains. GD_{1a}-like epitope expression may be an important virulence phenotype associated with the risk of developing GBS following campylobacter infection.

Guillain-Barré syndrome (GBS) is an acute, immune-mediated, postinfection disorder affecting the peripheral nervous system and is strongly associated with *Campylobacter jejuni* gastrointestinal (GI) infection (13). Expression of ganglioside-like mimicry in the outer core lipooligosaccharide (LOS) and development of an immune response in the host that cross-reacts with ganglioside-rich targets in the peripheral nerve are considered to be involved in the pathogenesis of *Campylobacter*-induced GBS (21). Anti-GD_{1a} antibodies are associated with the axonal (acute motor axonal neuropathy [AMAN]) form of GBS, whereas anti-GM_1 antibodies are seen in both AMAN and demyelinating (acute inflammatory demyelinating polyneuropathy [AIDP]) forms (12). Both AIDP and AMAN are associated with *C. jejuni* infection; however, patients with GBS following *Campylobacter* infection may be more likely to have axonal neuropathy (11, 12, 26, 28).

To determine whether GD_{1a}-like mimicry is specifically expressed in *C. jejuni* from patients with GBS, we analyzed a collection of isolates from GBS and enteritis (GI infection) patients for expression of both GD_{1a}- and GM_1-like mimicry.

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Isolates listed in Table 1 were collected from a variety of worldwide sources and were previously studied by multilocus enzyme electrophoresis and for GM_1-like mimicry (5, 23). The isolates from GBS patients are likely to represent both AMAN and AIDP forms of GBS. However, information on the type of GBS was available from only a limited number of patients and is noted in Table 1.

GM_1-like and GD_{1a}-like mimicries were determined using a dot blot assay that was validated for the detection of GM_1-like mimicry, as described previously (24). GM_1-like mimicry was detected using cholera toxin subunit B, which was labeled with horseradish peroxidase (Sigma, St. Louis, Mo.) and used at a concentration of 0.105 μg/ml. The GD_{1a}-like epitope was detected using an anti-GD_{1a} monoclonal antibody (clone, Gg101; isotype, immunoglobulin G1) produced in knockout mice defective in the production of endogenous complex gangliosides and characterized previously by Lunn et al. (17). Purified antibody was labeled with horseradish peroxidase as described by McIlhinney et al. (18) and used at a concentration of 0.035 μg/ml. The GD_{1a} binding assay was validated using control strains of known ganglioside mimicry, and binding assays using 12 different blots of each reference strain were used to calculate confidence intervals (CI). There was clear separation of binding between *C. jejuni* HS:3 (ATCC 43431), which does not mimic gangliosides, and the serotype reference strain (serostrain) HS:19 (ATCC 43446), which exhibits both GM_1- and GD_{1a}-like mimicry (24). The range of binding for the HS:19 reference strain was 192 to 235 U, whereas HS:3 had an upper 99% CI of 71 U. Serostrains HS:36 (ATCC 43456) and HS:1 (ATCC 43429) express GM_2 mimicry, with an upper 99% CI of 125 U. *Escherichia coli* (ATCC 35218) and *Salmonella enterica* serovar Typhimurium X4550 (provided by R. Curtiss, Washington University, St. Louis, Mo.) as negative controls showed a binding value of <20 U. Strains with binding values above 125 U were considered positive for the GD_{1a} epitope. The antibody was also strongly reactive against serostrain HS:4, which contains a 9:1 ratio of molecules bearing GD_{1a} to molecules bearing GM_1 in thin-layer chromatography (1). Fisher's exact test or the chi-square test (Yates' correction) was used to compare the differences between proportions (EpiInfo 2000, verion 1.1.2; Centers for Disease Control and Prevention, Atlanta, Ga.).

When isolates were analyzed for the expression of GM_1-like mimicry, there was no difference between GI and GBS isolates or between HS:19 and non-HS:19 serotypes ($P = 0.85$) (Table 2). Compared to GI isolates, GBS-associated isolates were significantly more likely to express a GD_{1a}-like epitope (78.6 versus 19.8%; $P < 0.0000001$; OR, 14.90; CI, 4.69 to 49.71). When isolates were analyzed according to serotype, HS:19

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TABLE 1. Isolates studied for GM_1- and GD_{1a}-like expression

Isolate[a]	HS serotype	Country	Disease	Type of mimicry[b]		Isolate[a]	HS serotype	Country	Disease	Type of mimicry[b]	
				GM_1	GD_{1a}					GM_1	GD_{1a}
HB93-6	2	China	GBS (AMAN)	−	+	INP10	19	Mexico	GI	−	−
DVL5783	2	Denmark	GI	−	−	INP15	19	Mexico	GI	+	−
DVL5808	2	Denmark	GI	+	−	INP53	19	Mexico	GI	−	−
DVL5752	2	Denmark	GI	+	−	INP64	19	Mexico	GI	−	−
DVL5837	2	Denmark	GI	−	−	INP25	19	Mexico	GI	−	+
DVL7796	2	Denmark	GI	+	−	INP24	19	Mexico	GBS	−	+
DVL5906	2	Denmark	GBS	−	+	INP7	19	Mexico	GBS	−	+
D3007	2	United States	GI	+	−	INP8	19	Mexico	GBS	+	+
D3027	2	United States	GI	−	−	INP23	19	Mexico	GBS	−	+
ATCC 43431	3	Canada	GI	−	−	159.83	19	South Africa	GI	+	−
DVL5775	4	Denmark	GI	−	−	331-82	19	South Africa	GI	−	−
DVL5834	4	Denmark	GI	+	−	93-84	19	South Africa	GI	+	+
DVL5758	4	Denmark	GI	+	−	D3002	19	United States	GI	+	−
INP44	4	Mexico	GI	−	−	D3083	19	United States	GI	+	−
INP50	4	Mexico	GI	−	−	D3145	19	United States	GI	+	−
HB93-10	5	China	GBS (AMAN)	+	+	D3180	19	United States	GI	+	−
DVL5569	5	Denmark	GI	−	−	D3468	19	United States	GI	+	−
DVL5305	5	Denmark	GI	−	−	D445	19	United States	GI	−	−
DVL5444	5	Denmark	GI	−	−	D450	19	United States	GI	−	−
DVL5611	5	Denmark	GI	−	−	D452	19	United States	GI	−	−
DVL5457	5	Denmark	GI	+	+	D3141	19	United States	GI	+	−
D3074	5	United States	GI	−	−	D3215	19	United States	GI	+	−
D3030	5	United States	GI	−	+	D3226	19	United States	GI	−	+
ATCC 43434	6	Canada	GI	−	−	D3088	19	United States	GI	−	+
NCTC 11828	6	United Kingdom	GI	−	−	ATCC 43429	23	Canada	GI	−	−
ATCC 43438	10	Canada	GI	−	−	ATCC 43456	36	Canada	GI	+	−
ATCC 43446	19	Canada	GI	+	+	HB97-34	37	China	GBS (AMAN)	+	−
98-3118	19	Canada	GBS	−	+	DVL5543	37	Denmark	GI	−	−
98-347	19	Canada	GBS	−	+	DVL5443	37	Denmark	GI	−	−
HB96-43	19	China	GBS (AMAN)	+	−	DVL5879	37	Denmark	GI	+	−
HB95-29	19	China	GBS (AMAN)	+	+	DVL5560	37	Denmark	GI	−	−
HB93-13	19	China	GBS (AMAN)	+	+	DVL5842	37	Denmark	GI	+	−
DVL5292	19	Denmark	GI	+	−	DVL5408	37	Denmark	GI	+	+
DVL5323	19	Denmark	GI	−	−	INP16	37	Mexico	GBS	−	+
DVL5549	19	Denmark	GI	+	−	DVL5558	41	Denmark	GI	+	−
DVL5632	19	Denmark	GI	−	−	DVL5600	41	Denmark	GI	−	−
DVL5433	19	Denmark	GI	−	−	DVL5671	41	Denmark	GI	−	−
DVL5172	19	Denmark	GI	+	+	DVL5724	41	Denmark	GI	−	−
DVL5194	19	Denmark	GI	+	+	INP59	41	Mexico	GBS	+	−
DVL5476	19	Denmark	GI	+	+	INP21	41	Mexico	GBS	−	+
DVL5553	19	Denmark	GI	+	+	D3017	45	United States	GI	−	−
DVL5112	19	Denmark	GI	+	+	HB96-35	53	China	GBS (AMAN)	+	+
84-158	19	Germany	GBS	−	+	DVL5795	1, 44	Denmark	GI	−	−
KB1428	19	Japan	GI	−	−	INP65	23, 36	Mexico	GI	−	−
KB1645	19	Japan	GI	−	−	DVL5550	4′[c]	Denmark	GI	−	−
KB697	19	Japan	GI	−	−	DVL5615	4′	Denmark	GI	+	−
KB761	19	Japan	GI	+	−	DVL5620	4′	Denmark	GI	+	−
KB1062	19	Japan	GI	−	+	DVL5514	4′	Denmark	GI	+	+
OH4382	19	Japan	GBS	+	−	DVL5529	4′	Denmark	GI	+	+
KB3449	19	Japan	GBS	+	+	DVL5610	4′	Denmark	GBS	−	−
KB3463	19	Japan	GBS	−	+	DVL5516	4′	Denmark	GBS	−	+
KB3473	19	Japan	GBS	+	+	JHU2	4′	United States	GBS (AIDP)	−	−
KB3482	19	Japan	GBS	−	+	INP66	$5^+, 5^-$	Mexico	GI	−	−
OH4384	19	Japan	GBS	+	+	INP67	$5^+, 5^-$	Mexico	GI	−	−
KB3466	19	Japan	GBS	−	+						

[a] ATCC, American Type Culture Collection; NCTC, National Collection of Type Cultures, London, United Kingdom.
[b] +, present; −, absent.
[c] 4′ refers to a complex that may include HS:4, -13, -16, -43, or -50.

isolates from GBS patients ($n = 17$) were associated with GD_{1a} expression significantly more often than GI infection-associated HS:19 isolates (88.2 versus 30.6%; $P = 0.0003$; OR, 17.05; CI, 2.89 to 130.72). For isolates of serotypes other than HS:19, GBS-associated isolates ($n = 11$) were also associated with GD_{1a} expression significantly more often than GI serotypes (63.6 versus 11.1%; $P = 0.0008$; OR, 14.00; CI, 2.44 to 91.03).

Also, we examined whether GD_{1a}-like expression was independent of GM_1-like mimicry. Eight of 28 GBS (28.6%) isolates and 11 of 81 GI (13.6%) isolates expressed both GM_1-

TABLE 2. Distribution of GD_{1a}- and GM_1-like mimicry in GBS- and GI-related isolates of *C. jejuni*

Type of mimicry	Isolates	Disease association		
		% of isolates that were from:		P^a
		GBS patients (n = 28)	GI patients (n = 81)	
GM_1	All	42.9	43.2	0.85 (NS)
	HS:19	47.1	52.8	0.924 (NS)
	Non-HS:19	36.4	35.6	0.61 (NS)
GD_{1a}	All	78.6	19.8	<0.0000001
	HS:19	88.2	30.6	0.0003
	Non HS:19	63.6	11.1	0.0008

[a] Fisher's exact test or the chi-square test with Yates' corection was used to compare the differences between proportions. NS, not significant.

and GD_{1a}-like structures, results that are not statistically different (P = 0.130; OR, 2.55; CI, 0.8 to 8.07). Expression of only GM_1-like mimicry was not associated with either GBS (14.3%) or GI isolates (29.6%) (P = 0.176; OR, 0.40; CI, 0.1 to 1.39). However, expression of only GD_{1a} was strongly associated with GBS-related isolates (50.0% for GBS isolates versus 6.2% for GI isolates; P = 0.00001; OR, 15.2; CI, 4.2 to 58.57). Expression of only GD_{1a} was independent of serotype and was significantly associated with GBS-related HS:19 isolates (52.9% for GBS isolates versus 11.1% for GI isolates; P = 0.0018; OR, 9.00; CI, 1.85 to 47.95) and non-HS:19 serotypes (45.4% for GBS isolates versus 2.2% for GI isolates; P = 0.0006; OR, 36.67; CI, 3.1 to 996.5).

Using PCR, we examined the presence of core LOS genes, *cgtA*, *cgtB*, and *cst-II*, associated with ganglioside mimicry in GBS- and GI infection-related *C. jejuni* isolates. Primer sets for each of the genes were developed based on previously published sequences (6, 15). The primers for *cgtA* were CgtAUp (5′ATA CGG GAG GGG CAT AAA G3′) and CgtADn (5′ATA AGC AAG CAA TCT CCT GGT T3′) (527 bp). The *cgtB* primers were CgtBUp (5′AGA GCA AGA TAT GAA GGT GTG AA3′) and CgtBDn (5′AAA CCA ACT GCA ACT CTT GAA T3′) (502 bp). Two primer sets were used to detect *cstII* based on the HS:2 (NCTC11168) and HS:19 (OH4384) sequences reported by Gilbert et al. (6). The primers used for *cstII* from HS:19 were Cst-IIUp (5′GTT ATT ATT GCT GGA AAT GGA CCA AGT 3′) and Cst-IIDn (5′ ACA TAT AGA CCC CTG AGG TAA TTC TTT GAT3′) (400 bp), and the primers used for HS:2 were Cst-IIUp (5′TTG GTA TGC GGT AAT GGA CCT A3′) and Cst-IIDn (5′CAG AGC CAC AGC TGT AGC ACA 3′) (417 bp). Amplification using either *cstII* primer was indicative of the presence of the *cstII* gene. As a control for each bacterial DNA preparation, *waaC*, a conserved heptosyltransferase gene involved in LOS biosynthesis, was also amplified.

The presence of the three genes *cst-II*, *cgtA*, and *cgtB* was strongly associated with GBS-related isolates, unlike with GI isolates (82.1 versus 45.7%; P = 0.001; OR, 5.47; CI, 1.74 to 18.34). There was no difference between GBS- and GI infection-related HS:19 isolates, as 98.1% of all HS:19 isolates contained these genes. However, GBS-related non-HS:19 isolates were more likely to contain these genes (54.5%) than were GI infection-related non-HS:19 isolates (2.2%) (P = 0.001).

The role of ganglioside-like mimicry in eliciting pathogenic host immune responses is not fully understood, but patients with GBS are more likely to mount a host response to these mimics than are patients with GI disease only (29, 33). *C. jejuni* strains have been shown to exhibit various types of ganglioside mimicry, including expression of GM_1-, GM_2-, GM_3-, GD_{1a}-, GD_{1b}, GD_2-, GD_3-, and GT_{1a}-like structures (20). In the present study, we examined both GM_1- and GD_{1a}-like expression in GBS- and GI infection-associated *C. jejuni* isolates that were collected from all over the world. GM_1-like mimicry was found not to be specific to isolates from either group of patients, which is consistent with our previous findings on the distribution of GM_1 mimicry in U.S. diarrheal isolates (24). Likewise, a detailed structural analysis of *C. jejuni* HS:19 isolates associated with GBS or GI infection showed that both could express GM_1 mimicry (19). Other studies have examined small numbers of isolates for the presence of ganglioside-type mimicry (25, 27, 31, 32, 36, 37); however, none have adequately assessed differences among GBS- and diarrhea-related strains.

Anti-GD_{1a} antibodies are highly associated with the AMAN form of GBS and are usually not generally produced in patients with AIDP (2, 12, 39). Other antibodies, including anti-GalNAc-GD_{1a} and anti-GD1b antibodies, have also been found to be associated with AMAN development (26). Using a specific monoclonal antibody directed against GD_{1a}, we showed that expression of GD_{1a}-like mimicry was strongly associated with GBS-related isolates. Moreover, GBS-related isolates of the HS:19 serotype and non-HS:19 serotypes were significantly more likely to express the GD_{1a}-like epitope than were GI infection-related isolates. The association of GD_{1a} expression with GBS-related isolates was independent of GM_1-type mimicry. Various *C. jejuni* HS serotypes have been isolated from patients with GBS, and some studies suggest that serotype HS:19 is overrepresented among patients with GBS in certain geographic locations but not in others (22). These findings suggest that expression of GD_{1a} may be a serotype-independent property linked to the ability of *C. jejuni* to induce pathogenic antibodies in susceptible hosts.

There may also be quantitative differences in the amounts of GD_{1a} expressed, as suggested by the observation that the HS:4 serotype expresses a 9:1 ratio of GD_{1a} moieties to GM_1 moieties, compared to a 1:1 ratio for the HS:19 serostrain (1). The expression of GD_{1a}-like mimicry in GBS-related isolates does not rule out the possibility that other types of mimicry may be involved in the pathogenesis of *Campylobacter*-induced GBS. In preliminary studies using previously described techniques (27), thin-layer chromatography immunostaining of several isolates with anti-GD_{1a} binding in the intermediate range suggest that GD1b-like mimicry may also be present (data not shown and reference 24).

While a GD_{1a}-like epitope was preferentially expressed in GBS-related isolates, some GI infection-related isolates expressed this epitope as well. The presence of this epitope, therefore, is not alone responsible for causing GBS. Host genetic susceptibility to developing GBS following exposure to a strain with this virulence phenotype is likely to be a critical factor (30, 35).

The genetic basis for ganglioside-type mimicry has been studied only recently, and it is clear that the mechanisms for producing ganglioside-like structures in LOS are complex and

undergo phase variation (7, 9, 10, 15, 16). We did not study the degree of phase-variable GD_{1a} expression in this study. Nevertheless, it is possible that phase-variable rates of GD_{1a} expression differ between GBS- and GI infection-related isolates. A few genes, *cst-II*, *cgtA*, and *cgtB*, appear to be critical in *C. jejuni* ganglioside mimicry expression (7, 9,10, 15, 16). In particular, *cst-II* (α-2,3 and/or α-2,3/α-2,8 sialyltransferase) has been shown to be involved in the addition of a terminal sialic acid residue that forms the GD_{1a} epitope (6). The *cgtA* gene product, β1,4-*N*-acetylgalactosyltransferase, and the *cgtB* gene product, β1,3-galactosyltransferase, add the substrates for sialylation to the LOS backbone.

We compared GBS- and GI infection-related isolates for the presence of these three genes and found that they were more strongly associated with GBS-related isolates than with uncomplicated GI isolates and that they were highly associated with the HS:19 serotype. The uniform presence of these genes in HS:19 isolates is not totally surprising since this serotype is highly clonal and infection with HS:19 is associated with an increased risk of GBS (22, 23). Of particular interest is the observation by Gilbert et al. (8) that a GBS-related HS:2 isolate was shown to possess the HS:19 LOS gene cluster, suggesting that this gene cluster may confer unique, still to be completely defined, virulence properties involved in GBS pathogenesis.

Molecular analysis of *C. jejuni* isolates from GBS and GI patients has been unable to differentiate between GI infection-related and GBS-related isolates (3–5, 23). The *cst-II* gene was found previously to be associated with a small number of GBS-related strains by van Belkum et al. (34). In contrast, the present study clearly identified a phenotype strongly associated with GBS-related isolates. The lack of relevant animal models has hampered studies of the role of ganglioside-like mimicry in inducing GBS; however, the recent description of the development of nerve pathology in rabbits immunized with gangliosides may be applicable to studies of *Campylobacter* in the near future (14, 38).

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