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Serum Antibodies against Gangliosides and *Campylobacter jejuni* Lipopolysaccharides in Miller Fisher Syndrome

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Seven patients with Miller Fisher syndrome (MFS), six in the acute phase and one in the recovery phase, were investigated for serum antibodies against gangliosides and purified lipopolysaccharides (LPS) from different strains of *Campylobacter jejuni*, including the MFS-associated serotypes O:2 and O:23. Immunoglobulin G antibodies against gangliosides GT1a and GQ1b were found in five of six patients in the acute phase of disease. Three of these patients also displayed antibodies to ganglioside GD2, a finding not previously reported for MFS. All anti-GT1a- and anti-GQ1b-seropositive patients showed antibody binding to *C. jejuni* LPS, predominantly to O:2 and O:23 LPS. Antibody cross-reactivity between gangliosides GT1a and GQ1b and O:2 and O:23 LPS was demonstrated by adsorption studies. This cross-reactivity between gangliosides and *C. jejuni* LPS, which is obviously due to oligosaccharide homologies, may be an important pathogenetic factor in the development of MFS after *C. jejuni* infection.

In 1956, Miller Fisher (9) described three patients with a syndrome of acute external ophthalmoplegia, ataxia, and absent tendon reflexes (Miller Fisher syndrome [MFS]). Based on common clinical features (6), MFS is generally regarded as a variant of Guillain-Barré syndrome (GBS), an inflammatory demyelinating polyneuropathy possibly mediated by autoimmune mechanisms. In both neurological diseases, serum antibodies against gangliosides have previously been observed. Around 30% of GBS cases display autoantibodies predominantly against ganglioside GM1 (21), whereas more than 90% of MFS patients show immunoglobulin G (IgG) antibodies against gangliosides GT1a and GQ1b (8, 22). Antibody titers decrease within 2 of 5 weeks of disease onset (7, 8, 23, 29). The high incidence of anti-GT1a anti-GQ1b, the time course of antibody titers, and the occurrence of GQ1b in human oculomotor nerve (8) suggest that anti-GT1a and anti-GQ1b autoantibodies contribute to the pathogenesis of MFS.

The association of GBS and MFS with preceding infections, particularly with *Campylobacter jejuni*, and the evidence of structural homologies between gangliosides and *C. jejuni* lipopolysaccharides (LPS) raise the question of whether molecular mimicry between bacterial and human antigens may trigger autoimmune mechanisms (17). By using the heat-stable O antigen typing scheme for *C. jejuni* (16), GBS has previously been reported to be linked with certain *C. jejuni* serotypes, with O:19 predominating over O:2 and O:4 (11, 15). In MFS, an association with serotypes O:2, O:10, and O:23 was found (10, 19, 27). Ganglioside-mimicking structures have been identified in the outer core oligosaccharide (OS) region of LPS from MFS- and GBS-linked *C. jejuni* serotypes. OS structures mimicking gangliosides GM1 and GD1a have previously been found in O:4 and O:19 LPS with *C. jejuni* serostrains (1–3, 5) and *C. jejuni* isolates from GBS patients (13, 30); recognition of these epitopes by antiganglioside antibodies has previously been reported (20, 25, 28, 31). An OS structure mimicking ganglioside GM2 was found in LPS from the *C. jejuni* serostrain for serotype O:23 (3); however, immunological cross-reactivity was not observed (28). An OS structure mimicking ganglioside GD3 was identified in LPS of *C. jejuni* serotype O:10 isolated from an MFS patient (19). Although the similarity between LPS from *C. jejuni* serostrain O:2 and gangliosides appears to be restricted to a disaccharide unit (4), recognition by antibodies against asialo-GM1 has previously been demonstrated (20). In addition, monoclonal antibody against ganglioside GQ1b has previously been shown to cross-react with O:2 LPS from MFS patient *C. jejuni* isolates (27).

To our knowledge, only two studies have reported MFS patient antibodies cross-reactive between GQ1b and *C. jejuni* antigens. In three MFS patients, antibody cross-reactivity with GQ1b and whole *C. jejuni* isolates was demonstrated (10); for one MFS patient, cross-reactivity between GQ1b and LPS from a *C. jejuni* serotype O:2 isolate has previously been reported (26). We studied the occurrence of serum antibodies against gangliosides in seven patients with MFS, and we examined their cross-reactivities with purified LPS from *C. jejuni* serostrains O:2, O:4, and O:19, as well as LPS from *C. jejuni* serotypes O:23 and O:41, isolated from an MFS patient and a GBS patient, respectively.

MATERIALS AND METHODS

Patients. Sera were obtained from seven patients with typical MFS (Table 1). All of them showed the triad of ataxia, areflexia, and ophthalmoplegia. Six patients were in the acute phase of the disease (between 5 and 18 days after the onset of neurological symptoms), and one patient was in the recovery phase (9 weeks after onset). Except for two cases, all patients developed MFS after an infection of either the gastrointestinal or respiratory tract. In patients 6 and 7, with enteritic diarrhea preceding MFS, *C. jejuni* was demonstrated by conventional bacteriological cultivation. The causative agents in patients 4 and 5, with antecedent respiratory infections, were not identified. For control investigations, sera were obtained from 10 GBS patients (6 in the acute phase of the disease) and from five healthy individuals.

Bacteria and *C. jejuni* LPS. *C. jejuni* serostrains O:2 (ATCC 43430), O:4 (ATCC 43432), and O:19 (ATCC 43446) were obtained from the American Type Culture Collection (Rockville, Md.). *C. jejuni* strains were isolated from stool specimens of an MFS patient and a GBS patient and identified (16) as serotypes O:23 and O:41, respectively. Strains were grown on blood agar under microaerophilic conditions, biomass was harvested, and LPS were isolated by phenol-water extraction as described previously (14).

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TABLE 1. Data for seven MFS patients

Patient no.	Age (yr)/sex[a]	Preceding infection[b]	Day of serum sampling[c]
1	12/M	GI	5
2	58/F	?	5
3	44/M	?	6
4	51/M	R	7
5	46/M	R	7
6	62/M	GI, *Cj*	18
7	29/M	GI, *Cj*	62

[a] M, male; F, female.
[b] GI, gastrointestinal tract; R, respiratory tract; *Cj*, *C. jejuni* infection; ?, unknown.
[c] After the onset of neurological symptoms (between 5 and 18 days, acute phase; 62 days, recovery phase).

Detection of antiganglioside antibodies. The binding of IgA, IgM, and IgG antibodies to gangliosides was investigated by thin-layer chromatography (TLC)–immunostaining. Gangliosides GT1a and GQ1b were purchased from IsoSep AB (Tullinge, Sweden); GM1, GM2, GD1a, GD1b, GD2, GD3, GT1b, and asialo-GM1 were from Sigma (St. Louis, Mo.). Gangliosides (0.2 to 0.5 μg/lane) were developed by TLC on precoated silica gel 60 glass plates (Merck, Darmstadt, Germany) with chloroform–methanol–0.2% $CaCl_2 \cdot 2H_2O$ (50:45:10 [vol/vol/vol]) as the solvent system (18) and visualized with resorcinol-HCl reagent. TLC-immunostaining was performed by the procedure of Saito et al. (18) and modified as follows. Developed TLC plates were dried for 30 min in a desiccator, dipped in 0.2% polyisobutyl-methacrylate (Aldrich, Steinheim, Germany) in *n*-hexane for 1.5 min, and dried as described above. Individual lanes were overlaid with patient or control serum diluted 1:100 in 0.3% gelatin–phosphate-buffered saline (PBS) (wt/vol; pH 7.4). Plates were incubated in a humid chamber for 1 h at room temperature, washed with PBS, and air dried for about 5 min. Lane contents were incubated with peroxidase-conjugated rabbit anti-human IgG, IgA, or IgM (Jackson, Westgrove, Pa.), diluted 1:500 in gelatin-PBS, for 2 h at room temperature and washed with PBS. Subsequently, the plate was dipped in a solution of 0.5 mg of 4-chloro-1-naphthol per ml and 0.04% H_2O_2 in methanol–phosphate-citrate buffer (pH 5.0) (1:5 [vol/vol]) until immunoreactants became visible. The substrate reaction was stopped by washing with PBS.

Detection of anti-*C. jejuni* LPS antibodies. The binding of IgA, IgM, and IgG antibodies to LPS from *C. jejuni* serotypes O:2, O:4, O:19, O:23, and O:41 was investigated by TLC-immunostaining as described above for gangliosides. LPS (0.5 to 1.0 μg/lane) were developed by TLC with *n*-propanol–water–25% NH_4OH (60:30:10 [vol/vol/vol]) as the solvent system (31). For reference purposes, LPS were visualized with resorcinol-HCl reagent.

Immunoadsorption of patient sera. For cross-reactivity studies, MFS patient sera were incubated with ganglioside GQ1b or GM1 (3 mg/ml) for 3 h at 4°C. Immunoprecipitates were removed by centrifugation (24,000 × *g*, 10 min), and adsorbed samples were tested at a final dilution of 1:100 for residual IgG binding activities to gangliosides and LPS by TLC-immunostaining.

RESULTS

Antibodies against gangliosides. Typical ganglioside TLC-immunostaining results with a patient serum sample are shown in Fig. 1. IgG from patient 4 showed strong binding to gangliosides GT1a, GQ1b, and GD2 and much weaker binding to GM1, GD1a, GD1b, and GD3. The results for all seven patients are summarized in Table 2. Five of six MFS patients in the acute phase of the disease had serum antibodies to gangliosides GT1a and GQ1b. In patients 3, 4, and 6, additional strong reactions with GD2 and weaker reactions with GM1, GD1a, and GD1b were detected. None of the patients had IgG antibodies against asialo-GM1, GM2, or GT1b or IgA or IgM antibodies against any gangliosides (data not shown). Antibody binding to GT1a and GQ1b was not detected either for patient 1 at days 5, 13, and 115 after the onset of neurological symptoms or for patient 7 in the recovery phase of the disease.

In the GBS control group, three patients showed serum IgG antibodies against GM1 and additional weak binding to GM2 (in two cases) or to GD1a and GD1b (in one case). None of these patients had antibodies against GT1a, GQ1b, GD2, or GD3. Sera of healthy individuals did not react with any of the gangliosides tested.

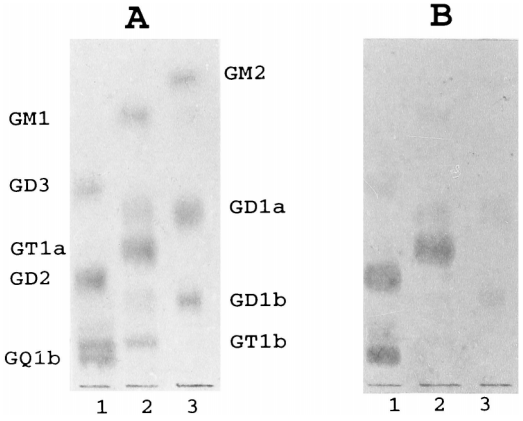

FIG. 1. Binding of an MFS patient serum sample to gangliosides by TLC of gangliosides (0.2 to 0.5 μg/lane). Lanes 1, GD3, GD2, GT1b, and GQ1b; lanes 2, GM1, GT1a, and GT1b; lanes 3, GM2, GD1a, and GD1b. (A) Ganglioside staining with resorcinol-HCl reagent; (B) binding of IgG from serum sample of patient 4 to gangliosides by TLC.

Antibodies to *C. jejuni* LPS. An example of TLC-immunostaining of *C. jejuni* LPS with a patient serum sample is shown in Fig. 2. IgG from patient 4 bound to *C. jejuni* O:2 and O:23 LPS and weakly to O:19 LPS, but not to O:4 and O:41 LPS. The results for all seven patients are summarized in Table 3. All five patients positive for anti-GT1a and anti-GQ1b antibodies (cases 2 to 6) also showed antibody reactions with *C. jejuni* LPS, whereas anti-GT1a- and anti-GQ1b-negative patients (cases 1 and 7) did not. Of the two patients with bacteriologically proven *C. jejuni* enteritis, patient 6 was positive and patient 7 was negative for LPS antibodies.

Table 3 shows clearly that antibody recognition of LPS from *C. jejuni* serotype O:2 and from at least one additional serotype occurred in all five antiganglioside-positive patients. Antibody reactivities with O:19 LPS were detected in sera from patients 3, 4, and 6; reactions with O:23 LPS were found in sera from patients 4 and 5 (strong reactions) and patients 2 and 3 (weak reactions). Only the serum sample of patient 3 showed antibody recognition of O:41 LPS. None of the patients showed IgG antibodies against O:4 LPS or IgA or IgM antibodies against any *C. jejuni* LPS tested (data not shown).

The three anti-GM1-positive GBS control patients also showed IgG reactivities with *C. jejuni* LPS, predominantly with O:19 and O:2 LPS. None of these patients had antibodies

TABLE 2. IgG antibodies against gangliosides in seven MFS patients

Patient no.	IgG reaction to ganglioside[a]						
	GM1	GD1a	GD1b	GD2	GD3	GT1a	GQ1b
1	−	−	−	−	−	−	−
2	−	−	−	−	−	++	++
3	+	+	+	++	−	++	++
4	+	+	+	++	+	++	++
5	−	−	−	−	−	++	++
6	+	+	+	++	−	++	++
7	−	−	−	−	−	−	−

[a] Staining: ++, strong; +, weak; −, no reaction. No reaction was detected with asialo-GM1, GM2, or GT1b for any of these patients.

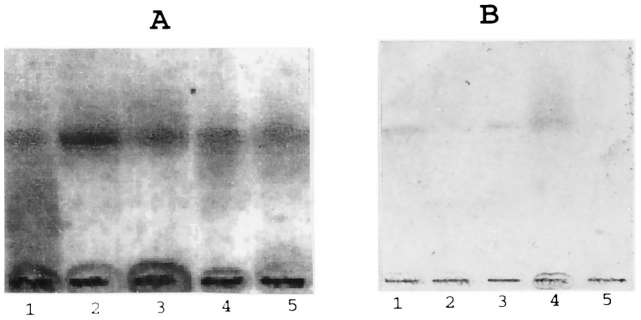

FIG. 2. Binding of an MFS patient serum sample to *C. jejuni* LPS by TLC of purified *C. jejuni* LPS (0.5 to 1.0 μg/lane). Lanes 1 through 5, LPS from *C. jejuni* O:2, O:4, O:19, O:23, and O:41, respectively. (A) *C. jejuni* LPS staining with resorcinol-HCl reagent; (B) binding of IgG from serum sample of patient 4 to purified *C. jejuni* LPS by TLC.

against O:23 LPS. Sera of healthy individuals did not react with any of the *C. jejuni* LPS tested.

Adsorption studies. Sera from patients 2 and 4 were preadsorbed with GQ1b and GM1 for controls and tested by TLC-immunostaining. For both patients, adsorption with GQ1b removed IgG binding to gangliosides GT1a and GQ1b and to O:2 and O:23 LPS. For patient 4, adsorption with GQ1b did not remove reactivity with GD2 or with O:19 LPS. Adsorption with GM1 had no effect on binding to gangliosides GT1a and GQ1b and O:2 and O:23 LPS.

DISCUSSION

Serum IgG antibodies against GT1a and GQ1b were demonstrated for five of six MFS patients in the acute phase of the disease but were not present in the recovery phase (patient 7). Three of the anti-GT1a- and anti-GQ1b-positive patients also showed strong antibody binding to GD2 and weaker binding to GD1a, GD1b, and GM1; for one patient, binding to GD3 was detected as well. Previous reports have shown antibody reactivities with GT1a and GQ1b in all seropositive patients and with GD1b, GD3, or both in about half of the cases (7, 8, 22, 24). To our knowledge, antibodies to GD2 in MFS patients have not been reported before. Although the MFS-related gangliosides are characterized by at least one disialosyl group α2-3 linked to galactose (Fig. 3), the antibody reactivities observed and the results from adsorption experiments suggest the occurrence of antibodies with slightly different specificities rather than cross-reactivity. Anti-GT1a- and anti-GQ1b-specific antibodies characteristic for MFS appear to recognize an OS moiety containing a terminal disialosyl group linked to the tetrasaccharide backbone of GT1a and GQ1b. Reactivity with GD2 in a subgroup of MFS patients seems to indicate the presence of additional antibodies recognizing an OS structure with an internal disialosyl group linked to the GD2 trisaccharide backbone. A predominant reactivity with GD2, compared to that with GD3, may suggest a role for GalNAcβ1-4 linked to galactose in epitope recognition. Weaker binding to GD1b and the lack of binding to GT1b may reflect increasing steric hindrance due to the addition of extra terminal sugar residues to the OS.

Serum IgG antibodies from the five anti-GT1a- and anti-GQ1b-positive patients were demonstrated to recognize *C. jejuni* LPS. An examination of antibody fine specificity for LPS from different *C. jejuni* serotypes showed a predominant recognition of O:2 LPS (five patients). *C. jejuni* serotype O:2 has previously been reported to be linked to MFS in patients with preceding enteritis (27) as well as to rare cases of GBS associated with *C. jejuni* infection (11). The structural similarity between LPS of *C. jejuni* serostrain O:2 (Fig. 3) and gangliosides appears to be confined to a Neu5Acα2-3Galβ1-disaccharide (4). However, the recognition of O:2 LPS by rabbit anti-asialo-GM1 antibodies, which was demonstrated in our previous study (20), and the reaction with mouse monoclonal anti-GQ1b antibody (27) suggest the presence of additional epitopes in O:2 LPS that mimic other structures in GQ1b.

Four of five anti-GT1a- and anti-GQ1b antibody-positive patients (cases 2 to 5) had a reaction with O:23 LPS in addition to recognition of O:2 LPS. O:23 LPS was extracted from a *C. jejuni* strain associated with the subsequent development of MFS in another patient, whose serum unfortunately was not available for our antibody studies. LPS from *C. jejuni* serostrain O:23 (Fig. 3) has previously been found to have a core OS with terminal regions mimicking those of GM2 (3). However, mouse monoclonal antibodies against GM2 and other gangliosides did not cross-react with O:23 LPS (28). In addition, sera from our patients 2 to 5 did not react with GM2. On the other hand, based on antibody cross-reactivity between GQ1b and whole bacterial isolates (10), it has previously been suggested that GQ1b-like epitopes are present in *C. jejuni* serotype O:23.

The three patients with antibodies against GT1a, GQ1b, GD2, and other gangliosides, including GM1 and GD1a, also displayed antibody binding to O:19 LPS. Previous reports have shown that antibodies against GM1 and GD1a cross-react with O:19 LPS (20, 25, 28, 31). LPS from *C. jejuni* serostrain O:19 has previously been found to yield two types of outer core OS molecules, with one mimicking GM1 and the other mimicking GD1a (1, 2). By using serotype O:19 isolates from GBS patients, GM1 or GD1a mimicry in the LPS outer core OS has previously been demonstrated as well (13, 30). However, two other GBS patient isolates have revealed structural homologies with GD3 and GT1a in serotype O:19 LPS core OS (1, 2). Thus, mimicry of particular gangliosides appears to be independent of *C. jejuni* serotype (1, 2, 19, 28).

Only one patient showed antibody recognition of O:41 LPS. No structural data for O:41 LPS are available.

C. jejuni infection prior to MFS may trigger a cross-reactive immune response via epitopes shared by gangliosides and *C. jejuni* LPS (3, 4, 19, 26, 27). In our study, this view was substantiated by adsorption experiments demonstrating cross-reactivity between antibodies against GT1a and GQ1b and antibodies against O:2 and O:23 LPS and by the fact that IgG from two anti-GT1a- and anti-GQ1b-negative patients did not react with the LPS tested. Of our seven patients, culture-proven *C. jejuni* enteritis preceded MFS in cases 6 and 7; however, serotyping was not performed with bacterial isolates. Patient 6

TABLE 3. IgG antibodies against LPS of different *C. jejuni* serotypes in seven MFS patients

Patient no.	IgG reaction to LPS from *C. jejuni* serotype[a]				
	O:2	O:4	O:19	O:23	O:41
1	−	−	−	−	−
2	++	−	−	+	−
3	++	−	+	+	+
4	+	−	+	++	−
5	++	−	−	++	−
6	++	−	+	−	−
7	−	−	−	−	−

[a] Staining: ++, strong; +, weak; −, no reaction.

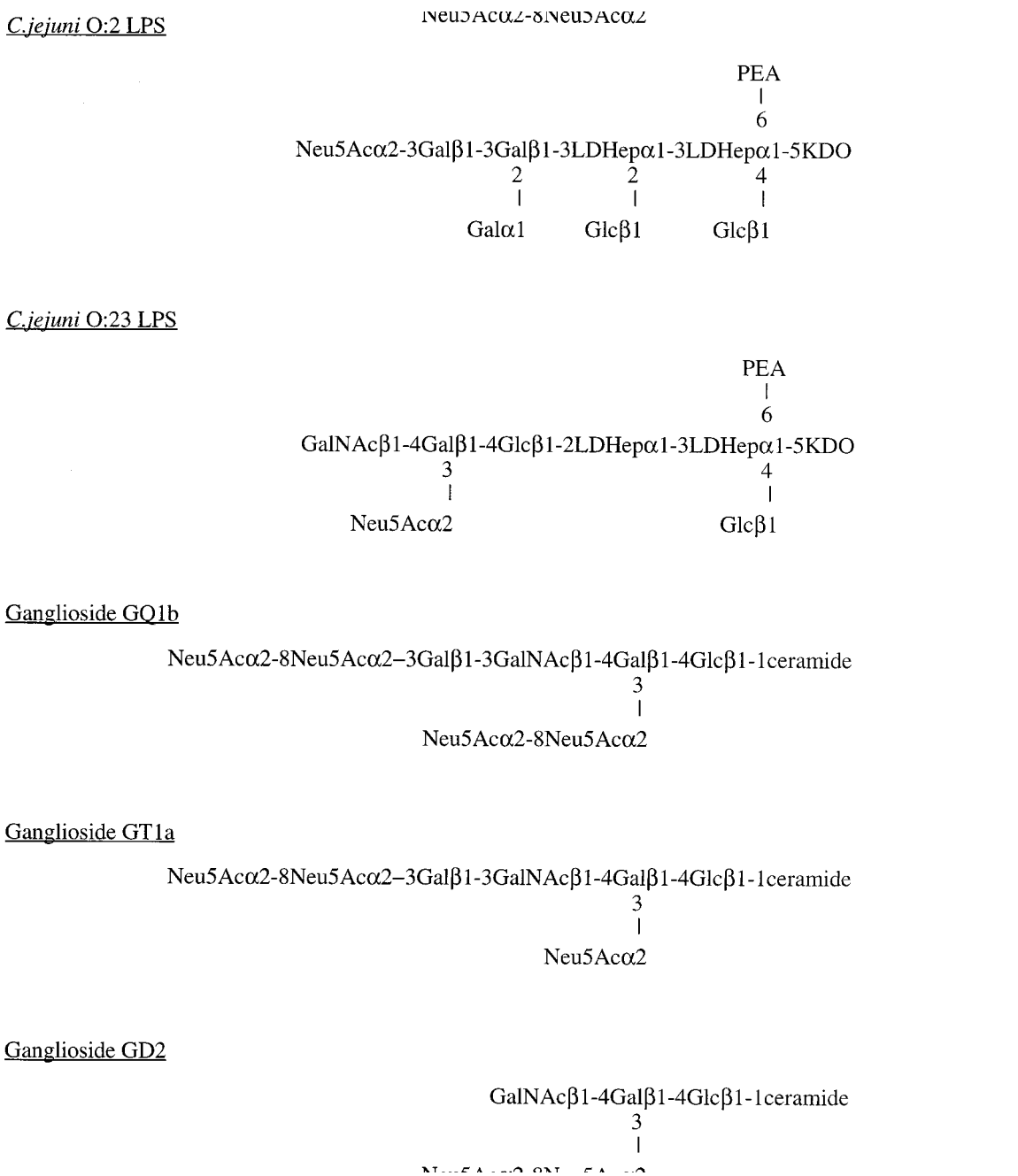

FIG. 3. Molecular structures of LPS core OSs from MFS-associated *C. jejuni* serotypes in comparison to structures of MFS-related gangliosides. Abbreviations: PEA, *O*-phosphoethanolamine; KDO, 3-deoxy-D-*manno*-2-octulosonic acid; LDHep, L-*glycero*-D-*manno*-heptose; Glc, glucose; Gal, galactose; GalNAc, *N*-acetylgalactosamine; Neu5Ac, *N*-acetylneuraminic (sialic) acid.

showed IgG antibodies recognizing gangliosides (predominantly GT1a, GQ1b, and GD2) and LPS from *C. jejuni* serotypes O:2 and O:19. On the other hand, patient 7 was negative for antibodies against gangliosides and LPS, probably due to late serum sampling (9 weeks after disease onset).

The antibody cross-reactivity between purified O:2 and O:23 LPS and gangliosides GT1a and GQ1b demonstrated in our study with MFS patient sera substantiates characteristic ganglioside mimicry by LPS in MFS-associated *C. jejuni* strains, which may be an essential pathomechanism in the development of MFS after antecedent *C. jejuni* infection. The origin of antiganglioside antibodies in MFS cases not related to *C. jejuni* infection is a completely open question. However, a number of gram-negative mucosal pathogens other than *C. jejuni* have previously been reported to express LPS-mimicking glycosphingolipids (12).

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