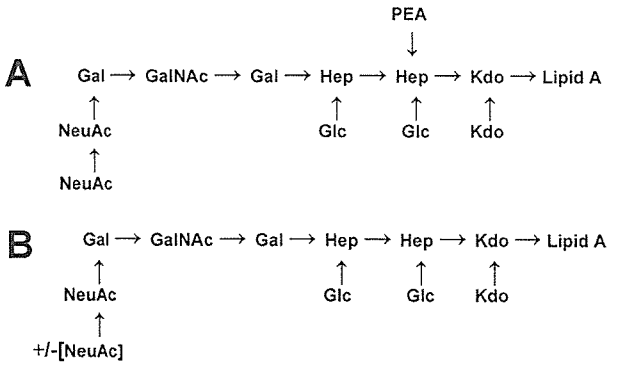

Figure 2. Proposed lipo-oligosaccharide outer core structures based on capillary-electrophoresis electrospray ionization mass spectrometry analysis of O*-deacylated lipo-oligosaccharide samples from* Campylobacter jejuni *isolates. (A) GC033 (Fisher syndrome) and GC124 (overlapping Bickerstaff brainstem encephalitis and Guillain–Barré syndrome); (B) GC057 (acute ophthalmoparesis). Gal = galactose; NeuAc =* N*-acetylneuraminic acid; GalNAc =* N*-acetylgalactosamine; Hep = L-glycero-D-manno-heptose; Glc = glucose; Kdo = 3-deoxy-D-manno-2-octulosonic acid; PEA = phosphoethanolamine.*

only the terminal galactose is substituted by sialic acid because GC057 also has a Cj1135 allele that can transfer glucose to heptose II in its inner core (see above and GenBank accession number DQ438950). Tandem mass spectrometry data also was consistent with the absence of phosphoethanolamine or phosphate on heptose I (which is linked to the 3-deoxy-D-manno-2-octulosonic acid) of the GC057 LOS. Heptose I is substituted by a phosphate or a phosphoethanolamine in all *C jejuni* LOS structures so far reported.[20] Consequently, the absence of these substitutions on the heptose I of the LOS of *C jejuni* GC057 is an important observation.

Discussion. Serologic determinations may include false-positive cases, and *C jejuni* isolation is the gold standard for the diagnosis of bacterial infections. Over a 9-year period, we found 139 patients from whom *C jejuni* was isolated and whose medical histories were available for clinical analysis, although the latent period between preceding intestinal infection and the neuropathy onset often exceeds the excretion period of viable *C jejuni* cells in stools.[1] GBS, FS, MSR-preserved GBS, FS/GBS, BBE, BBE/GBS, AO, ataxic GBS, acute oropharyngeal palsy, and CIDP were diagnosed. Encephalopathy after *C jejuni* enteritis has been reported,[21] but no *C jejuni* isolates were found in 290 patients who had encephalopathy, encephalitis, or acute disseminated encephalomyelitis.

By chance, *C jejuni* enteritis may be concurrent with various diseases. When the bacterium is isolated from patients who have neurologic disorders, it is difficult to judge whether it had a causative role. Epidemiologic studies, however, have shown that *C jejuni* infection is related to GBS and FS,[10,22] and experimental studies suggest that antiganglioside IgG antibodies induced by ganglioside-mimicking *C jejuni* LOS cause both GBS and FS.[9,23] Our study has showed that each *C jejuni* LOS was recognized by the IgGs from patients with MSR-preserved GBS or FS-related conditions, indicative that as in GBS and FS, IgG antibodies induced by a ganglioside-like LOS are active in the development of those conditions. In contrast, LOS was not recognized by the IgG from a CIDP patient. Moreover, because only one *C jejuni* strain was isolated from more than 1,000 patients with CIDP, isolation might have occurred by chance. Our observations do not support the speculation that *C jejuni* infection induces the development of CIDP.[24,25]

Patients who experienced acute paralytic syndrome after gastrointestinal illness but had normal to brisk MSR have been reported, but the nosologic position of the syndrome is not clear.[26] We earlier reported four *C jejuni*–isolate patients who had acute progressive motor weakness and preserved MSR.[27] They had AMAN and anti-GM1 IgG antibodies, as did patients who had GBS subsequent to *C jejuni* enteritis.[2] We therefore proposed that the diagnostic criteria for GBS be extended to require hyporeflexia or areflexia as a hallmark. This, our larger study, showed that the clinical, serologic, and bacteriologic features of GBS are similar to those of MSR-preserved GBS, supportive evidence that both conditions are part of a continuous spectrum. Predominantly the HS:19 and *cst-II* (Thr51) strains were isolated from the MSR-preserved GBS as well as GBS patients,[5] and the GM1 or GD1a epitope was expressed in both of these *C jejuni* isolates. Moreover, anti-GM1 and anti-GD1a IgG antibodies were positive in both conditions. The hyperreflexia mechanism in AMAN is not known, but dysfunction of the inhibitory system via spinal interneurons may increase motor neuron excitability.[28] Inflammation of the spinal anterior roots may lead to disruption of the blood–CNS barrier, allowing antiganglioside antibodies access to antigens near anterior horn cells, especially in intramedullary collateral branches to the inhibitory interneurons. These findings suggest that host factors such as antibody accessibility, rather than bacterial ones, determine MSR.

Because the clinical and serologic features of FS are similar to those of FS/GBS, BBE, BBE/GBS, AO, ataxic GBS, and acute oropharyngeal palsy, the latter conditions have been considered to be FS related. Moreover, in each condition, antecedent *C jejuni* infection has been suggested serologically. Several patients from whom *C jejuni* was isolated have been reported. Our study provides evidence that these are FS-related conditions from the bacterial as well as the patients' standpoint.

Because of areflexia and CSF albuminocytologic dissociation, FS is considered a GBS variant.[29] This is strongly indicated by clinical observations that some patients who present with FS progress to GBS.[30] Moreover, it is supported by our serologic observations that some FS/GBS patients carry IgG an-

tibodies against GM1 and GD1a, as well as against GQ1b, which are reasonable findings. For example, a GT1a-like LOS is synthesized by Cst-II (Asn51) via GM1-like and GD1a-like LOSs, and an FS isolate (CF93-6) carries GM1-like and GD1a-like LOSs as well as a GT1a-like LOS.[8,10] The results shown in tables 1 and 2 suggest that *C jejuni* strains bearing *cst-II* (Asn51) induce the synthesis of anti-GM1 or anti-GD1a IgG antibodies, as well as anti-GQ1b/GT1a IgG antibodies, and that FS/GBS develops in some patients, whereas the same strains may induce only anti-GQ1b/GT1a IgG antibodies and the development of FS in others. Host genetic factors may determine which autoantibodies and clinical presentation occur.

BBE is characterized by consciousness disturbance as well as ophthalmoplegia and ataxia. The nosologic relationship of BBE to FS has long been debated. Anti-GQ1b IgG antibodies are present in BBE as in FS.[4,31] This was confirmed in patients with *C jejuni*–isolated BBE in our study. The immunologic profile common to FS and BBE supports a common pathogenesis. BBE etiology is speculated to be similar to that of GBS based on evidence of prodromal upper respiratory infection, areflexia, and CSF albuminocytologic dissociation.[32] Some patients experience limb weakness, considered the result of overlapping AMAN.[33] These clinical findings indicate that BBE and GBS are closely related, as are BBE and FS. Our study showed that the bacterial characteristics of a BBE isolate and BBE/GBS isolates were those of FS, not GBS isolates. The three BBE and BBE/GBS isolates belonged to the HS:2 or HS:4-complex and had the GQ1b epitope characteristic of FS isolates.[5] This is evidence that BBE and FS comprise parts of a continuous spectrum. BBE can be positioned as FS associated, having the apparent CNS sign of consciousness disturbance. Rather than bacterial factors, host factors such as antibody accessibility may determine whether the clinical presentation is FS or BBE, as in GBS and MSR-preserved GBS. As in FS that overlaps GBS, host genetic factors may determine the autoantibodies produced and whether the clinical presentation is BBE or BBE/GBS.

Acute onset of external ophthalmoplegia is a cardinal FS feature.[29] Four-fifths of FS cases studied started with diplopia, and the median period for the disappearance of ataxia was 1 month, and that of ophthalmoplegia was 3 months.[30] This temporal profile suggests that AO without ataxia is a mild form of FS, which is supported by serologic observations that patients with AO as well as those with FS carry anti-GQ1b IgG antibodies.[4,34] Our study confirmed that *C jejuni*–isolate AO patients had anti-GQ1b IgG antibodies. One AO isolate (GC057) belonged to HS:2 and had *cst-II* (Asn51) and a GQ1b epitope, characteristic of FS isolates.[5] These AO bacterial features are further evidence that AO and FS are parts of a continuous spectrum. Host rather than bacterial factors, such as the amounts or affinities of autoantibodies produced, may determine whether the clinical presentation is AO or FS.

Ataxic GBS, originally described by Richter,[17] is characterized by severe ataxia of the cerebellar type with no or minimal ophthalmoplegia. Clinical findings of hyporeflexia or areflexia, distal paresthesias, and CSF albuminocytologic dissociation indicate that the condition is a GBS variant. Some patients with ataxic GBS carry anti-GQ1b IgG antibodies.[35] The fact that ataxic GBS and FS have an autoantibody in common suggests that they form a continuous spectrum. Patient 23 with ataxic GBS also had anti-GQ1b IgG antibodies, and the isolate (GC216) had the *cst-II* (Asn51) genotype and expressed a GQ1b epitope on the LOS. Bacterial findings also support the speculation that ataxic GBS and FS are parts of a continuous spectrum, and that host rather than bacterial factors determine whether the clinical presentation is ataxic GBS or FS. Interestingly, the ganglioside composition of the neuromuscular junctions differs among mouse strains.[36] Some humans may not express GQ1b in their oculomotor nerves, although most do, as well as in their primary sensory neurons.[4,37] Immunohistochemical investigations of a large number of autopsy case studies are needed to clarify this.

One-fourth of patients with FS studied had bulbar palsy,[30] but acute oropharyngeal palsy is characterized by oropharyngeal weakness without ophthalmoplegia and limb weakness.[18] The acute oropharyngeal palsy patients carried anti-GQ1b/GT1a IgG antibodies. *C jejuni* was isolated from Patient 24, who had anti-GQ1b/GT1a IgG antibodies. That isolate (GC183), which belonged to the HS:4-complex, had the *cst-II* (Asn51) genotype and a GQ1b epitope on the LOS. Another isolate (GC229) had the *cst-II* (Thr51) genotype and did not carry a GQ1b epitope, but Patient 25 had anti-GQ1b IgG antibodies and serum IgG bound to its LOS. Whether the GC229 isolate actually functions in the induction of anti-GQ1b antibodies is unknown. Immunochemical analyses have shown that patients' lower cranial nerves had both GQ1b and GT1a,[38] but some humans may not express GQ1b in their oculomotor nerves (as discussed above). Host factors, such as antigen distribution, may determine whether the clinical presentation is AO, ataxic GBS, or acute oropharyngeal palsy.

Mass spectrometry showed that three *C jejuni* isolates from FS, BBE/GBS, and AO patients had GD1c-like LOS with terminal trisaccharides identical to those of GQ1b and GT1a (figures 2 and E-1). Another *C jejuni* strain (PG 836) isolated from a patient with FS also had a GD1c-like LOS.[12] These findings are further evidence that BBE/GBS and AO are related to FS and that host rather than bacterial factors determine the clinical presentation. In conclusion, the bacterial characteristics of FS are similar to those of FS/GBS, BBE, BBE/GBS, AO, ataxic GBS, and acute oropharyngeal palsy—additional evidence that these are FS-

related conditions. The bacterial genotype defines whether GBS, FS, or the related conditions will develop with a role for the patient in defining the specific clinical presentation.

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特集 移植治療に伴う神経合併症

造血幹細胞移植後GVHD（急性，慢性）に伴う末梢神経障害*

清水 潤**

Key Words：graft-versus-host disease（GVHD），neuropathy

GVHDについて

Graft-versus-host disease（GVHD）は，移植骨髄中に含まれるTリンパ球またはその前駆細胞が患者の種々の細胞を非自己と認識することにより生じる[1]．とくに同種骨髄移植に特異的な問題で50～70％に発症し，約1/3は重症となるとされる．

急性GVHDでは，Th_1細胞が病態の中核をなし，その機序としては，移植前処置による化学療法や放射線照射により障害を受けたホストの細胞がIL1，TNFα，INFγなどの各種サイトカインを分泌した上に，ドナーおよびホストの抗原提示細胞（antigen presenting cell：APC）がドナー由来のT細胞の活性化と増殖をうながし，活性化したドナーT細胞がホスト細胞のアポトーシスを誘導して臓器障害をきたすと考えられている．主な標的臓器は皮膚，消化管，肝臓であるが，眼，口腔粘膜の障害をきたすこともあり，通常移植後100日以内に起こる．診断上罹患臓器の生検が重要であり，皮膚生検が行われることが多い．

慢性GVHDの発症機序は不明な点が多いが，移植前処置や急性GVHDの結果，胸腺で自己反応性T細胞が除去されないためにトレランス機構の破綻をきたし，Th_2細胞の活性化とTh_2タイプのサイトカイン分泌が亢進し，その結果，自己反応性T細胞や自己反応性B細胞により産生された自己抗体により臓器の機能障害と線維化が起こると考えられている．

移植後100～450日に発症し，Sjögren症候群，強皮症，原発性胆汁性肝硬変などの自己免疫疾患に類似した臨床症状を呈し，広範型で初期治療が奏効しない場合は，重症感染の合併や原疾患の再発によりしばしば死の転帰をとる．

GVHDの治療としては，ステロイドやシクロスポリン，タクロリムスなどの免疫抑制剤が用いられる．

GVHDに伴う末梢神経障害

出現頻度は稀である．また，GVHDが直接的に末梢神経障害をひき起こしているかに関しては確かな証拠はまだない[19][20]．間接的な証拠としては，他のGVHD症状から示される病勢に伴い，末梢神経障害の病態が推移することが根拠となる．臨床における診断の場においては，cytomegalovirus（CMV）の活性化やその他のウイルスの感染もありうるため，臨床の場ではこれらの関連した末梢神経障害や傍腫瘍症候群としての末梢神経障害である可能性も考慮に入れる必要がある．

表1には，骨髄幹細胞移植後のGVHDの出現を伴い，末梢神経障害を起こしてきた症例報告をあげる[2]～[17]．この中にはCMVや*Campylobacter*

* Peripheral neuropathy in graft-versus-host disease（GVHD）after bone marrow trasplantation.

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表 1 Review of the literature

Auther	Patient Age/Sex	Underlying disorder	latency	Type of neuropathy	Treatment	Course
Granena (1983)[2]	15/M	AML	1M	subacute polyneuropathy	NI	improved
Wiznitzer (1984)[3]	NI	NI	NI	Peroneal, meralgia paresthesia	NI	improved
Maguire (1989)[4]	6/NI	malignant osteopetrosis	NI	CIDP	NI	NI
Greenspan (1990)[5]	35/M	AML	16M	Painful sensory with cramp	AZP, CS, PSL	Improved
Openshaw (1991)[6]	36/M	CML	6Y before	CIDP relapse	PP, PSL, CS, IVIG	Died
	21/M	Hodgkin's lymphoma	1Y before	CIDP relapse	PP, PSL, CS, IVIG	Died
Eliashiv (1991)[7]	34/F	ALL	1M	GBS	CP, PSL	Improved
Amato (1993)[8]	31/M	CML	6M	demyelinating neuropathy	PSL, AZP, CS, IVIG	Improved
	49/M	CML	8M	demyelinating neuropathy	PP, PSL, CS	Improved
	29/M	aplastic anemia	14D	demyelinating neuropathy	PSL, CS, IVIG	Improved
	43/M	non-Hodgkin's lymphoma	1M	demyelinating neuropathy	PP, PSL, IVIG	Improved
Hagensee (1994)[9]	57/M	myelodysplasia	1Y	GBS	IVIG	Improved
Perry (1994)[10]	42/M	CML	4M	GBS	PP	Improved
Liedtke (1994)[11]	40/M	CML	3M	GBS	IVIG	Improved
Wen (1997)[12]	34/M	CML	4M	GBS	PP	Improved
	59/F	CML	11M	GBS	PP	Died
Gabriel (1999)[13]	43/F	CML	3Y	vasculitic neuropathy	PSL	Improved
Nagashima (2001)[14]	32/M	non-Hodgkin's lymphoma	5Y	demyelinating neuropathy	mPSL	Improved
Al-Shekhlee (2001)[15]	49/F	CML	3Y	sensory mononeuropathy multiplex	PSL, IVIG	Improved
Mulrooney (2003)[16]	23/F	α-Mannosidosis	4M	axonal polyneuropathy	PP	Improved
Matsumoto (2005)[17]	47/M	ALL	1Y	demyelinating neuropathy	IVIG	Improved

NI : not indicated, AML : acute myelogenous leukemia, CML : chronic myelogenous leukemia, ALL : acute lymphocytic leukemia, CIDP : chronic inflammatory demyelinating polyneuropathy, GBS : Guillain-Barré syndrome, PSL : predonisolne, AZP : azathioprin, CS : cyclosporin, IGIG : intravenous immunoglobulin, PP : plasmapheresis, mPLS : methylprednisolone.

*jejuni*の感染を伴っているもの[9)~11)]や，GVHDと末梢神経障害の病勢が必ずしも一致していないもの[16)]，移植後から末梢神経障害の出現までの期間の長いもの[13)~15)]，感覚神経障害の分布が皮膚硬化と関連している例[15)]も含まれ，病態が均一ではない可能性がある．また，血管炎を伴った例[15)]に関しては，GVHDとの関連に関しての疑問が提示されている[18)]．

GVHDに伴う末梢神経障害の過去の報告を大きく分けると，慢性GVHDに伴い出現するタイプとT細胞の機能異常に伴い出現するGuillain-Barré症候群(GBS)のタイプの二つに分けられる[19)]．慢性GVHDに伴うものには，電気生理的に軸索障害のパターンを示し感覚運動型の末梢神経障害を示すタイプと[5)16)]，電気生理的に脱髄を示す脱髄性末梢神経障害のタイプが知られている．また，脱髄性の中には左右非対称の症状の出現をみる例[6)17)]もあり，機序の異なったものが含まれる可

能性がある．GBSタイプのものの出現時期は，移植後1カ月[7]のものから11カ月後[12]のものまであり，いずれも急性の進行性の四肢麻痺を示し，髄液での蛋白細胞解離を認めている．この中には再発性の症例もあり[11]，シクロスポリンの病態への関与も考慮すべきと考えられる[19]．一方，先行して存在したchronic inflammatory demyelinating polyneuropathy(CIDP)が骨髄移植後に増悪した例の報告もされている[6]．

過去の報告はいずれもGVHDの存在とともに末梢神経障害が出現または増悪を示し，免疫抑制剤の投与や治療により症状の改善を認めたために，GVHDの末梢神経障害への関与を推測している．しかし，GVHDの活動性との関連についての記載の不明確なものも多く，今後の症例の蓄積と個々の症例における注意深い解析が必要であろう．

移植に伴う末梢神経障害および鑑別すべき病態

骨髄移植前に用いられる化学療法剤であるvincristine, etoposide, cytosine arabinoside, cisplatinに加えGVHDの予防として用いられるシクロスポリン自体によっても末梢神経障害が出現しうるので鑑別が必要である[21]．また，もともと遺伝性末梢神経障害があり，これらの薬物の使用により症状が急速に顕在化する場合もあるので注意が必要である．

CMVの末梢神経感染やその他のウイルス感染に誘発された末梢神経障害も鑑別が必要であるが，実際上は困難な場合が多い．全身状態が悪い場合にはcritical illness neuropathyも鑑別にあがる．

症状からの鑑別では，進行性の筋力低下を認める場合にはGVHDに伴う筋炎や重症筋無力症も鑑別にあがる[19][20]．神経根の支配領域に一致した筋力低下や感覚異常を認める場合には，原疾患の髄膜や神経根への浸潤，帯状疱疹ウイルスの活性化，原疾患が悪性リンパ腫である場合にはそれによる傍腫瘍性の病態を鑑別する必要がある．外眼筋の麻痺を認めた場合には，現疾患の髄膜浸潤，重症筋無力症を鑑別にあげるがシクロスポリンによるものも報告されている[22]．一方，原疾患の再発や感染の合併なしに，可逆性の脳神経麻痺を顔面神経や聴神経に生じ，短期間のステロイド投与で症状が改善する症例もしばしば経験される[19]．腓骨神経麻痺や尺骨神経麻痺をGVHDの時期に一致して認めることがあり，このような場合には全身的な末梢神経障害の存在の有無に関しての精査が必要である．また，稀な合併症として血小板減少の状態で神経内への出血が単麻痺を起こした例[23]の報告がある．一方，慢性GVHDの治療として用いられるthalidemideにより運動感覚障害型の末梢神経障害を生じうるので注意が必要である[19][20]．

GVHDに伴う末梢神経障害は過去に約20例の報告があるが，GVHDが直接的に末梢神経障害出現機序に関与しているかに関しては不確実な点が多い．臨床の場においては個々の症例において可能性のある種々の原因を丁寧に除外診断することが必要である．

GVHDに伴う末梢神経障害の病態解明には，今後の病理検討を含めたより確かな症例報告や再現可能な動物実験での検討がされることが必要であろう．

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