

# 博士學位論文

インフルエンザウイルスを先行感染とする  
GBS の臨床的特徴と抗糖脂質抗体の解析

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Doctoral Dissertation

Guillain-Barré syndrome and related diseases after  
influenza virus infection

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論文題目

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神経病態制御学

# Guillain-Barré syndrome and related diseases after influenza virus infection

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## Abstract

### Objective

We examined the clinical and serologic features of Guillain-Barré syndrome (GBS)-related diseases (GBSRDs), including GBS, Fisher syndrome (FS), and Bickerstaff brainstem encephalitis (BBE), after influenza virus infection (GBSRD-I) to reveal potential underlying autoimmune mechanisms.

### Methods

We retrospectively investigated the presence of antiglycolipid antibodies against 11 glycolipids and the clinical features of 63 patients with GBSRD-I. Autoantibody profiles and clinical features were compared with those of 82 patients with GBSRDs after *Campylobacter jejuni* infection (GBSRD-C).

### Results

The anti-GQ1b seropositivity rate was significantly higher, whereas the GM1 and GD1a seropositivity rates were significantly lower in GBSRD-I compared with GBSRD-C. Anti-GQ1b and anti-GT1a were the most frequently detected antiglycolipid antibodies in GBSRD-I (both 15/63, 24%). Consequently, FS was more frequent in GBSRD-I than GBSRD-C (22% vs 9%,  $p < 0.05$ ). In addition, as for GBS, cranial nerve deficits, sensory disturbances, and ataxia were more frequent in the cases after influenza infection (GBS-I) than in those after *C. jejuni* infection (GBS-C) (46% vs 15%, 75% vs 46%, and 29% vs 4%, respectively; all  $p < 0.01$ ). Nerve conduction studies revealed acute inflammatory demyelinating polyneuropathy (AIDP) in 60% of patients with GBS-I but only 25% of patients with GBS-C ( $p < 0.01$ ).

### Conclusions

Anti-GQ1b antibodies are the most frequently detected antibodies in GBSRD-I. Compared with GBS-C, GBS-I is characterized by AIDP predominance and frequent presence of cranial nerve involvement and ataxia.

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## Glossary

**AIDP** = acute inflammatory demyelinating polyneuropathy; **AMAN** = acute motor axonal neuropathy; **BBE** = Bickerstaff brainstem encephalitis; **FS** = Fisher syndrome; **GBS** = Guillain-Barré syndrome; **GBS-C** = Guillain-Barré syndrome after *C. jejuni* infection; **GBS-I** = Guillain-Barré syndrome after influenza virus infection; **GBSRD** = Guillain-Barré syndrome-related disease; **GBSRD-C** = Guillain-Barré syndrome-related disease after *C. jejuni* infection; **GBSRD-I** = Guillain-Barré syndrome-related disease after influenza virus infection; **HA** = hemagglutinin; **NA** = neuraminidase; **NCS** = nerve conduction study; **RIDT** = rapid influenza diagnostic test.

Guillain-Barré syndrome (GBS) is an acute acquired autoimmune disorder of the peripheral nerves that frequently develops after infection. For instance, antecedent infection such as *Campylobacter jejuni*, cytomegalovirus, or *Mycoplasma pneumoniae* is observed in approximately 70% of patients with GBS. Alternatively, GBS following influenza virus infection (GBS-I) is relatively rare.<sup>1</sup> However, influenza virus infection is a common respiratory syndrome across all age groups. Influenza is also known to cause neurologic complications such as encephalitis, encephalopathy, and Reye syndrome that require differential diagnosis.<sup>2</sup> In addition, several reports have shown that influenza virus infection or influenza-like illness can also cause Fisher syndrome (FS) and Bickerstaff brainstem encephalitis (BBE),<sup>3–5</sup> which are caused by the pathogenetic mechanisms similar to those of GBS. Here, we call GBS, FS, and BBE as GBS-related diseases (GBSRDs).

Antiglycolipid antibodies are elevated in GBSRD and are strongly implicated in the pathogenesis. Antibodies against GM1 on the neuronal membrane ganglioside are often detected in GBS after *C. jejuni* infection, and antibodies to galactocerebroside (Gal-C) are often detected in neurologic diseases following *M. pneumoniae* infection.<sup>6,7</sup> The structures of these carbohydrates are similar to carbohydrates expressed by the infectious agents, suggesting that a form of molecular mimicry is responsible for GBS-associated autoimmunity.<sup>8,9</sup> In contrast to GBS associated with *C. jejuni* and *M. pneumoniae* infection, the clinical and serologic features of GBSRD and GBS after influenza virus infection (GBSRD-I and GBS-I, respectively) have not been described in detail. The purpose of this study is to investigate the unique clinical and serologic features of GBSRD-I and GBS-I.

## Methods

### Patients with GBSRD-I

We collected clinical information and acute-phase serum samples from consecutive patients who are diagnosed with GBSRD-I. These serum samples were sent to our laboratory from multiple hospitals in Japan between October 2009 and February 2017 for the examination of antiglycolipid antibodies. GBS and BBE were diagnosed according to previously presented criteria,<sup>10,11</sup> and FS was diagnosed according to the clinical triad of acute progressive ophthalmoplegia, ataxia, and areflexia without limb weakness or impairment of consciousness. Patients with the FS triad and limb weakness were

included in the GBS subgroup. In all patients with GBSRD, influenza virus infection was diagnosed by an immunochromatography-based rapid influenza diagnostic test (RIDT) within 4 weeks of the onset of symptoms. Immunochromatography-based RIDT detects nucleoprotein, which is one of the most abundant proteins in influenza virus and has fewer mutations than hemagglutinin (HA) and neuraminidase (NA). Although there are some differences in the detection rate, RIDT can detect various subtypes of influenza virus such as H1N1, H3N2, type B seasonal viruses, and pandemic H1N1 2009 viruses.<sup>12</sup> The sensitivity of the RIDTs is approximately 60%, and the specificity is higher than 95%.<sup>13</sup> Patients with GBSRD-I with antecedent gastrointestinal infectious symptoms were excluded from the study.

### Clinical and electrophysiological assessment

The clinical and electrophysiological data of each patient with GBS were obtained retrospectively from the original attending neurologist or pediatrician using a questionnaire. According to the Ho criteria, nerve conduction study (NCS) findings were used to classify cases as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), or unclassified.<sup>14</sup> NCSs were

**Table 1** Demographic and basic clinical features of the GBSRD-I and GBSRD-C groups

	GBSRD-I (n = 63)	GBSRD-C (n = 82)	p Values
Age, median [range] (y)	40 [3–83]	30.5 [3–87]	NS
Sex (male/female)	36/27	41/41	NS
Type of influenza virus (A/B/unknown)	37/17/10 <sup>a</sup>	NA	
GBS/FS/BBE	48/14/1	74/7/1	<0.05 <sup>b</sup>
Delay between infection and GBSRD onset median [range] (d)	(n = 61) <sup>c</sup> 10 [2–28]	(n = 76) <sup>c</sup> 9 [2–28]	NS

Abbreviations: BBE = Bickerstaff brainstem encephalitis; FS = Fisher syndrome; GBS = Guillain-Barré syndrome; GBSRD = Guillain-Barré syndrome-related disease; GBSRD-C = Guillain-Barré syndrome-related disease after *C. jejuni*; GBSRD-I = Guillain-Barré syndrome-related disease after influenza; NA = not applicable; NS = not significant.

<sup>a</sup> One patient was infected with both A and B influenza viruses. The number of days until onset was 8 after influenza A and 18 after influenza B.

<sup>b</sup> FS was significantly more frequent in GBSRD-I than GBSRD-C.

<sup>c</sup> In the GBSRD-I group, the patient with both influenza A and B and a patient with unclear delay from influenza to GBS onset were excluded (n = 2 of 63). In the GBSRD-C group, patients with unclear delay between influenza and GBS onset were excluded (n = 6 of 82).

performed at each participating hospital in a median of 8.5 days (range [1–20] days) after GBS symptom onset.

### Antiglycolipid antibodies

Serum IgG antibodies to 11 glycolipid antigens (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, GT1a, Gal-C, and GalNAc-GD1a) were examined in all patients by ELISA, as previously described.<sup>15</sup>

### Patients with GBSRD-C

Clinical and serologic features of GBSRD-I and GBS-I were compared with those of GBSRD and GBS after *C. jejuni* infection (GBSRD-C and GBS-C, respectively). The antiglycolipid antibodies of these patients with GBSRD-C were tested in our laboratory between September 2012 and April 2017. *C. jejuni* infection was diagnosed by fecal culture or *C. jejuni* antibody test.

### Statistical analysis

Differences in proportions were evaluated using the  $\chi^2$  test or Fisher exact test, and differences in the median were evaluated using the Mann-Whitney *U* test.  $p < 0.05$  (2 tailed) was considered significant for all tests. Statistical calculations were performed using SPSS version 2.0 (IBM, Japan).

### Study approval and patient consent

This study was approved by the Internal Review Board of Kindai University Faculty of Medicine. All participants provided written informed consent.

### Data availability

Anonymized data not published within the article will be shared by request from any qualified investigator.

## Results

### Comparison of GBS subtype and antiglycolipid antibody profile between GBSRD-I and GBSRD-C

The classic form of GBS (GBS-I or GBS-C according to the antecedent pathogen) was the most common disease subtype in both GBSRD-I and GBSRD-C groups (48/63 [76%] vs 74/82 [90%]), while BBE was rare in both groups (1 patient per group). In contrast, FS was significantly more prevalent in the GBSRD-I group compared with the GBSRD-C group (14/63 [22%] vs 7/82 [9%],  $p = 0.02$ ).

Antiglycolipid antibodies were detected more frequently in patients with GBSRD-C than in patients with GBSRD-I (51/82 [62%] vs 25/63 [40%];  $p < 0.01$ ) (table 1). There were also significant differences in seropositivity rates for specific antiglycolipid antibodies between groups. Anti-GM1 antibody was substantially more common in GBSRD-C than in GBSRD-I (24/82 [29%] vs 3/63 [5%];  $p < 0.01$ ). Similarly, seropositivity for anti-GD1a was more frequent in GBSRD-C (18/62 [22%] vs 1/63 [2%];  $p < 0.01$ ). In contrast, anti-GQ1b was significantly more frequent in GBSRD-I than in GBSRD-C (15/63 [24%] vs 7/82 [9%];  $p < 0.05$ ). Anti-GT1a was also relatively common in GBSRD-I (24%), although the seropositivity rate did not

**Table 2** Comparison of antiglycolipid antibody profile between patients with GBSRD-I and GBSRD-C

IgG antibody positive	GBSRD-I				GBSRD-C				p Values (GBSRD-I vs GBSRD-C)
	All (n = 63)	GBS-I (n = 48)	FS-I (n = 14)	BBE-I (n = 1)	All (n = 82)	GBS-C (n = 74)	FS-C (n = 7)	BBE-C (n = 1)	
Overall, n (%)	25 (40%)	14 (29%)	10 (71%)	1 (100%)	51 (62%)	44 (59%)	6 (86%)	1 (100%)	<0.01
GM1	3 (5%)	3 (6%)	0 (0%)	0 (0%)	24 (29%)	23 (31%)	1 (14%)	0 (0%)	<0.01
GM2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (6%)	5 (7%)	0 (0%)	0 (0%)	NS
GM3	1 (2%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NS
GD1a	1 (2%)	1 (2%)	0 (0%)	0 (0%)	18 (22%)	16 (22%)	1 (14%)	1 (100%)	<0.01
GD1b	9 (14%)	7 (15%)	2 (13%)	0 (0%)	12 (15%)	12 (16%)	0 (0%)	0 (0%)	NS
GD3	2 (3%)	0 (0%)	1 (7%)	1 (100%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	NS
GT1a	15 (24%)	4 (8%)	10 (71%)	1 (100%)	15 (18%)	9 (12%)	5 (71%)	1 (100%)	NS
GT1b	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4%)	1 (1%)	1 (14%)	1 (100%)	NS
GQ1b	15 (24%)	4 (8%)	10 (71%)	1 (100%)	7 (9%)	2 (3%)	4 (57%)	1 (100%)	<0.05
GalNAc-GD1a	8 (13%)	6 (13%)	1 (7%)	1 (100%)	17 (21%)	16 (22%)	1 (14%)	0 (0%)	NS
Gal-C	3 (5%)	3 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (14%)	0 (0%)	NS

Abbreviations: BBE-C = Bickerstaff brainstem encephalitis after *C. jejuni* infection; BBE-I = Bickerstaff brainstem encephalitis after influenza virus infection; FS-C = Fisher syndrome after *C. jejuni* infection; FS-I = Fisher syndrome after influenza virus infection; GBS-C = Guillain-Barré syndrome after *C. jejuni* infection; GBS-I = Guillain-Barré syndrome after influenza virus infection; GBSRD-C = Guillain-Barré syndrome-related disease after *C. jejuni* infection; GBSRD-I = Guillain-Barré syndrome-related disease after influenza virus infection; NA = not applicable; NS = not significant.

**Table 3** Comparison of clinical characteristic between patients with GBS-I and GBS-C

Features	GBS-I (n = 48)	GBS-C (n = 74)	p Value
Age median [range] (y)	32 [3–83]	35.5 [3–87]	NS
Sex (male/female)	26/22	37/37	NS
Antiglycolipid antibody positive	14 (29%)	44 (59%)	<0.01
Cranial nerve deficits	22 (46%)	11 (15%)	<0.01
III, IV, and VI	8	2	
V	3	1	
VII	13	8	
IX and X	9	8	
XI and XII	7	5	
Severe muscle weakness (MMT <3)	20 (42%)	33 (45%)	NS
Sensory disturbances	36 (75%)	34 (46%)	<0.01
Ataxia	14 (29%)	3 (4%)	<0.01
Autonomic disturbance	10 (21%)	15 (20%)	NS
Peak FG	(n = 46)	(n = 59)	
FG1	4	10	
FG2	11	12	
FG3	11	5	
FG4	13	26	
FG5	7	6	NS
FG6	0	0	
Electrophysiological examination	(n = 30)	(n = 55)	
AMAN	0 (0%)	13 (24%)	<0.01
AIDP	18 (60%)	14 (25%)	<0.01
Unclassified	12 (40%)	28 (51%)	NS

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; FG = functional grade; GBS-C = Guillain-Barré syndrome after *C. jejuni* infection; GBS-I = Guillain-Barré syndrome after influenza virus infection; MMT = manual muscle testing; NS = not significant.

differ significantly from patients with GBSRD-C (18%). Among the 15 patients with GBSRD-I seropositive for anti-GQ1b, 10 were diagnosed with FS. In patients with GBS-I, anti-GD1b was the most frequently detected autoantibody (7/48, 15%) (table 2).

### Clinical features of GBS-I

The clinical features of GBS-I (n = 48) and GBS-C are summarized in table 3. Compared with patients with GBS-C, patients with GBS-I demonstrated a substantially lower antiglycolipid antibody seropositivity rate (29% vs 59%,  $p < 0.01$ ). Conversely, cranial nerve deficits, sensory disturbances, and

ataxia were significantly more frequent in GBS-I than in GBS-C (46% vs 15%, 75% vs 46%, and 29% vs 4%, respectively;  $p < 0.01$ ). There were no significant differences in age, sex ratio, autonomic disturbance frequency, and the requirement for artificial ventilation between GBS-I and GBS-C subgroups.

We also obtained the NCS findings from 30 patients with GBS-I. According to the Ho criteria, 18 cases were classified as AIDP and 12 were unclassified, whereas no case was classified as AMAN. The proportion with AIDP was significantly higher in the GBS-I subgroup than in the GBS-C subgroup ( $p < 0.01$ ). Among patients with GBS-I, there were no significant differences in demographic or clinical features between those infected with influenza virus A or B.

## Discussion

GBSRD is presented after not only gastrointestinal infection but also upper respiratory infection. However, most of the antecedent infectious agents of upper respiratory infection are not identified. In the present study, we focused on influenza virus infection and report the distinct clinical and serologic features of GBSRD-I and GBS-I.

Anti-GQ1b and anti-GT1a were the most frequently detected antiglycolipid antibodies in GBSRD-I. GQ1b is densely localized in the paranodal regions of III, IV, and VI human cranial nerves. Therefore, anti-GQ1b antibody can cause ophthalmoplegia, which is one of the major symptoms of FS.<sup>16</sup> In accord with this, FS was more frequent in GBSRD-I than GBSRD-C.

Compared with GBS-C, GBS-I is characterized by more frequent cranial nerve deficits, sensory disturbances, and ataxia. In addition, NCS findings revealed demyelinating neuropathy in a higher proportion of GBS-I cases than GBS-C cases. Furthermore, the frequency of AIDP was higher in GBS-I than in all GBS cases previously reported by a prospective cohort study in Japan (60% vs 40%).<sup>17</sup> This is compatible with the results that GM1 and GD1a seropositivity rates were significantly lower in GBSRD-I compared with GBSRD-C. Besides, compared with cases with GBSRDs after *M. pneumoniae* infection (GBSRD-M) reported recently,<sup>7</sup> the clinical and serologic features of GBSRD-I were somewhat different from those of GBSRD-M, in which the anti-GQ1b antibody positive rate and the frequency of FS cases were lower, and the anti-Gal-C antibody positive rate was higher than in GBSRD-I.

Previous reports (summarized in table 4) also found more frequent cranial nerve deficits (8/19, 42%) and sensory disturbance (15/19, 79%) in GBS-I. Moreover, these NCSs revealed demyelinating neuropathy in some patients with GBS-I (5/13, 38%), whereas axonal neuropathy was relatively less common (2/13, 15%).<sup>1,18–23</sup> Those are in accord with the current findings.

**Table 4** Clinical summary of previously reported patients with GBS-I

	No. of Patients	Type of influenza virus (no. of patients)	Duration until onset from infections	Cranial nerve deficits	Sensory disturbances	NCS (no. of patients)	Antiganglioside antibodies
Jacobs et al. <sup>1</sup>	3	A (2); B (1)	ND	ND	ND	ND	ND
Sivadon-Tardy et al., 2009 <sup>18</sup>	14	A (10); B (4)	12 d [3–30]	– (8); + (6)	– (1); + (13)	Demyelinating (4); normal (1); equivocal (3); ND (6)	Negative
Simpson et al., 2009 <sup>19</sup>	1	A	7 d	—	+	Equivocal	GD1b
Chaari et al., 2010 <sup>20</sup>	1	A	15 d	+	+	Reduction of MCV and prolonged DL	ND
Kutlesa et al., 2010 <sup>21</sup>	1	A	15 d	—	—	Axonal	GM1, GD1a, and GD1b
Cortese et al., 2012 <sup>22</sup>	1	A	1 d	+	—	Normal	Negative
Vasconcelos et al., 2012 <sup>23</sup>	1	A	7 d	—	—	Axonal	Negative

Abbreviations: DL = distal latency; GBS = Guillain-Barré syndrome; MCV = motor nerve conduction velocity; NCS = nerve conduction study; ND = not described.

Influenza viruses A and B are wrapped by a lipid bilayer envelope containing various glycoproteins, including HA and NA. Therefore, antiglycolipid antibodies may be produced by influenza virus infection because of possible molecular mimicry between glycoproteins of influenza viruses and glycolipids localized in human peripheral nerves.

The main limitation of this study is that we could not completely exclude the possible coexistence of other infections. Selection bias by attending physicians also could exist. In addition, we could not evaluate whether the severity and infection period of influenza virus infection are associated with the severity of GBS-I because the study was retrospectively conducted. A future prospective study is needed to clarify those issues. However, this study enrolled a relatively large number of patients, all with confirmed influenza infection. Therefore, clinical characteristics should reflect GBS-I and GBSRD-I.

In conclusion, antiglycolipid antibodies are detected in some GBSRD-I cases, and anti-GQ1b and anti-GT1a antibodies are the most frequent. Compared with GBS-C, GBS-I is characterized by more frequent AIDP, cranial nerve deficits, sensory disturbances, and ataxia. Further investigation is required to clarify the pathomechanisms of GBSRD-I.

### Author contributions

M. Yamana has contributed to acquisition, analysis, and interpretation of data and drafted the manuscript. M. Kuwahara has analyzed and interpreted data and also participated in drafting the manuscript and revising it. Y. Fukumoto, K. Yoshikawa, and K. Takada have contributed to acquisition of data. S. Kusunoki has made substantial contributions to conception and design of the study and also revised the

manuscript critically for important intellectual content. S. Kusunoki made final approval of the manuscript.

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### Disclosure

None of the authors report any disclosures relevant to the manuscript. Disclosures available: [Neurology.org/NN](https://www.neurology.org/NN).

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