Continuous Spectrum of Pharyngeal-Cervical-Brachial Variant of Guillain-Barré Syndrome

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**Background:** Pharyngeal-cervical-brachial weakness (PCB) is considered a variant of Guillain-Barré syndrome (GBS). Because of its rarity, there have been no studies of large numbers of patients with PCB.

**Objective:** To clarify the nosological classification of PCB.

**Design:** Retrospective study.

**Setting:** Academic research.

**Patients:** Medical records were reviewed of patients who manifested progressive weakness of the pharynx, neck, and upper limbs within 4 weeks of initial onset.

**Main Outcome Measures:** Clinical features were analyzed, and antecedent infections and antiganglioside antibodies were investigated.

**Results:** Diagnoses for 100 patients were “pure PCB” (n=13), PCB with preserved muscle stretch reflexes (n=8), GBS overlap (n=48), Fisher syndrome overlap (n=26), and Bickerstaff brainstem encephalitis overlap (n=5). Serological test results showed that 31.0% of antecedent infections in PCB were caused by *Campylobacter jejuni*. Of the antiganglioside antibodies tested, anti-GT1a IgG antibodies were positive in 51.0% of the patients. Anti-GQ1b IgG antibodies (a serological marker of Fisher syndrome and Bickerstaff brainstem encephalitis) were positive in 39.0%. The IgG antibodies to GM1, GM1b, GD1a, or GalNAc-GD1a (serological markers of an axonal GBS subtype) were positive in 27.0%.

**Conclusion:** This large study identified the clinical profiles of PCB. Clinical overlapping, frequent C. jejuni infection, and common antiganglioside antibodies present in PCB, GBS, Fisher syndrome, and Bickerstaff brainstem encephalitis provide conclusive evidence that PCB and these conditions form a continuous spectrum.

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FS and BBE are associated with anti-GQ1b IgG antibodies, which cross-react with GT1a.\textsuperscript{3,13} In contrast, IgG antibodies to GM1b, GD1a, and GT1a have been reported in several patients with PCB.\textsuperscript{9,14-16} Because of its rarity, we are aware of no comprehensive studies of large numbers of patients with PCB. For this study, we reviewed the medical records of 100 patients in whom there was acute progressive weakness of the pharynx, neck, and upper limbs, and we investigated the clinical and serological profiles of the patients to establish the nosological classification of PCB.

**METHODS**

**PATIENTS**

From August 1, 1999, to February 29, 2004, we received about 6600 requests from Japanese physicians to test serum ganglioside antibodies in patients who had various neurological disorders. Patients’ clinical features were reviewed in their medical records, and additional questionnaires were obtained from each primary physician to identify cases in which progressive weakness of the pharynx, neck, and upper limbs had developed within 4 weeks of the initial onset. Information on age, sex, initial symptoms, cerebrospinal fluid findings, antecedent infectious symptoms, and neurological signs during the illness were obtained. Approval of the ethics committee at our university was obtained to perform this study.

Clinical features used in the diagnosis of “pure PCB” were (1) progressive weakness predominant in the neck, arms, and oropharyngeal muscles by 4 weeks after the initial onset, (2) hyporeflexia or areflexia in the arms, and (3) no weakness in the legs. Patients with PCB-like symptoms who had normal to brisk muscle stretch reflexes (MSR) throughout the illness were categorized as having PCB with preserved MSR, and those who had leg weakness were categorized as having GBS overlapping PCB (GBS overlap). Based on the findings of Fisher\textsuperscript{17} and Bickerstaff,\textsuperscript{17} progressive symmetric external ophthalmoplegia and ataxia by 4 weeks was a required clinical feature for the diagnoses of FS and BBE. Hyporeflexia or areflexia and clear consciousness were required for the diagnosis of FS, whereas impaired consciousness was required for the diagnosis of BBE. Hyporeflexia and areflexia were not exclusion criteria for the diagnosis of BBE, as half of the original cases had hyporeflexia or areflexia.\textsuperscript{17} Patients with PCB-like symptoms who showed ophthalmoplegia, ataxia, and alert consciousness were classified as having PCB overlapping FS (FS overlap), and patients with ophthalmoplegia, ataxia, and altered consciousness were classified as having PCB overlapping BBE (BBE overlap). For the diagnosis of these conditions, the following must be excluded: botulism, diphtheria, brainstem tumor, neuro-Behçet disease, multiple sclerosis, polymyositis, myasthenia gravis, Wernicke encephalopathy, toxic or metabolic neuropathy, acute disseminated encephalomyelitis, and vascular disease involving the brainstem.\textsuperscript{18}

**SEROLOGICAL STUDIES**

Evidence of recent infection by *C jejuni*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, cytomegalovirus, or Epstein-Barr virus was assayed serologically as previously described.\textsuperscript{8} Serum samples from patients with GBS (n=73), patients with FS (n=73), and hospital control subjects (n=73) were the controls used in the statistical analysis.

Serum IgG antibodies to GT1a, GQ1b, GM1, GM1b, GD1a, and GalNAc-GD1a were measured by enzyme-linked immunoabsorbent assay as described elsewhere.\textsuperscript{19} In this study, serum was considered positive for antiganglioside antibodies when the absorbance value was 0.5 or higher at a dilution of 1:500 because this high cutoff level gives high specificity, as reported elsewhere.\textsuperscript{20} An absorption study was performed as described previously.\textsuperscript{21} The absorption rate was expressed as the percentage of absorbance obtained with and without absorption.

**STATISTICAL ANALYSIS**

Differences in medians were examined using the Mann-Whitney test. Differences in frequencies between groups were compared by χ² or Fisher exact test (2-tailed) using commercially available statistical software (SPSS 12.0J; SPSS Inc, Chicago, Illinois). A difference was considered statistically significant at *P* < .05.

**RESULTS**

One hundred patients (median age, 43 years [56 men and 44 women]) had manifested acutely progressive weakness of the pharynx, neck, and arms (Table 1). Limb weakness invariably predominated in the arms. A history of antecedent illness was present in 81.0% of the patients (upper respiratory tract infectious symptoms only in 51.0%, gastrointestinal tract symptoms only in 10.0%, and both symptoms in 20.0%). The most frequent initial symptom was arm weakness (29.0%), and the second most frequent initial symptoms were dysphagia (17.0%) and diplopia (17.0%). Other symptoms were blepharoptosis (n=4), facial weakness (n=4), photophobia (n=3), dysgeusia (n=1), and psychotic manifestation (n=1). During their illnesses, 91.0% of the patients had hyporeflexia or areflexia in the arms and 86.0% in the legs, 60.0% had superficial sense impairment (59.0% in the arms and 38.0% in the legs), 55.0% had external ophthalmoparesis, and 43.0% had ataxia. Predominant arm weakness was proximal in 47.0% and distal in 28.0%. Mild leg weakness (Medical Research Council scale score, 4) was present in 37.0%, and severe leg weakness (Medical Research Council scale score, ≤3) was present in 31.0%. Autonomic dysfunction occurred in 20.0%, including abnormal heart rate (n=9) and blood pressure (n=2), urination (n=8) and defecation (n=2) difficulties, orthostatic hypotension (n=1), abnormal perspiration (n=1), Horner syndrome (n=1), and arrhythmia (n=1). The median number of days to nadir was 7, and endotracheal intubation was used for 27.0% of the patients. Cerebrospinal fluid albuminocytological dissociation was present in 42.0%.

Diagnoses were pure PCB (n=13), PCB with preserved MRS (n=8), GBS overlap (n=48), FS overlap (n=26), and BBE overlap (n=5) (Table 1). The sex ratio, days to nadir, age distribution, frequency of antecedent illness, and frequencies of endotracheal intubation and cerebrospinal fluid albuminocytological dissociation did not statistically significantly differ between patients with pure PCB and patients with the other conditions.
ANTECEDENT INFECTIONS

Serological evidence of recent C. jejuni (in 31.0% of patients) and cytomegalovirus (in 6.0% of patients) infections was statistically significantly more common in the patients with PCB than in the hospital control subjects (P < .001 and P = .04, respectively), whereas the differences among the other infections were statistically non-significant (Table 2). The frequency of recent C. jejuni infection was similar to that in patients with GBS (31.5%) but higher than that in patients with FS (20.5%). The frequency of recent H. influenzae infection was 1.0% in patients with PCB, which was similar to that in patients with GBS (2.7%) but was statistically significantly lower than that in patients with FS (8.2%) (P = .04).
The median age was statistically significantly younger in 31 patients with PCB having serological evidence of recent *C. jejuni* infection than in 69 patients with PCB without it (35 vs 50 years, *P* = .047). External ophthalmoplegia was less common in the patients with *C. jejuni*-related PCB than in the others (38.7% vs 62.3%), as was sensory disturbance (45.2% vs 75.4%).

### ANTIGANGLIOSIDE ANTIBODIES

Of the antiganglioside antibodies tested, 68.0% of 100 patients with PCB had at least 1. Anti-GT1a IgG antibodies were found in 51.0% of 100 patients with PCB (Table 3); anti-GQ1b IgG antibodies were positive in 37 of the 51 patients carrying the anti-GT1a antibodies. Fifty-one serum samples with anti-GT1a IgG antibodies were absorbed effectively (35 vs 50 years, *P* = .047). External ophthalmoplegia was less common in the patients with *C. jejuni*-related PCB than in the others (38.7% vs 62.3%), as was sensory disturbance (45.2% vs 75.4%).

#### Table 3. Antiganglioside IgG Antibodies in Pharyngeal-Cervical-Brachial Weakness (PCB)<sup>3</sup>

<table>
<thead>
<tr>
<th>IgG Antibody</th>
<th>Total (N = 100)</th>
<th>Pure PCB (n = 13)</th>
<th>GBS With Preserved MRS (n = 8)</th>
<th>FS Overlap (n = 26)</th>
<th>BBE Overlap (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a</td>
<td>51 (51.0)</td>
<td>6 (46.2)</td>
<td>3 (37.5)</td>
<td>18 (37.5)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>GQ1b</td>
<td>39 (39.0)</td>
<td>4 (30.8)</td>
<td>1 (12.5)</td>
<td>12 (25.0)</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td>GM1</td>
<td>10 (10.0)</td>
<td>1 (7.7)</td>
<td>0</td>
<td>8 (16.7)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>GM1b</td>
<td>16 (16.0)</td>
<td>1 (7.7)</td>
<td>0</td>
<td>11 (22.9)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>GD1a</td>
<td>12 (12.0)</td>
<td>1 (7.7)</td>
<td>1 (12.5)</td>
<td>8 (16.7)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>GalNAc-GD1a</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>GM1, GM1b, GD1a, or GalNAc-GD1a</td>
<td>27 (27.0)</td>
<td>2 (15.4)</td>
<td>1 (12.5)</td>
<td>18 (37.5)</td>
<td>4 (15.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BBE, Bickerstaff brainstem encephalitis; FS, Fisher syndrome; GBS, Guillain-Barré syndrome; MRS, muscle stretch reflexes.

<sup>3</sup>Data are given as number (percentage).

An initial study of GBS by Ropper<sup>4</sup> stressed the presence of shoulder weakness, but our large study shows that arm weakness is not always proximally dominant in PCB. Based on diagnostic criteria by Ropper et al.,<sup>22</sup> the presence of diaphragm weakness, (almost) normal strength and tendon reflexes in the legs, and minimal or no sensory deficit is required. However, there was hip flexion weakness in patients 1 and 2 in the study by Ropper,<sup>4</sup> and in patient 2 there was generalized areflexia. Diaphragm weakness was not noted in patient 3. Therefore, we believe that the presence of diaphragm weakness and normal leg tendon reflexes is not essential for the diagnosis of PCB. A bulbar variant of GBS has been proposed in which muscle weakness of the face, tongue, or deglutition at onset is noted.<sup>23</sup> Frequent facial muscle involvement has been reported in patients with a lower cranial nerve form of GBS.<sup>24</sup> However, only 4 of our patients with PCB initially experienced facial weakness, although 64 patients did so at a later stage. Therefore, facial weakness at onset is not an essential criterion for PCB.

During a 6-year period, we identified 100 patients with PCB. Diagnoses for these patients were pure PCB, PCB with preserved MRS, GBS overlap, FS overlap, and BBE overlap. Although referral bias may exist, the objective of this study was not to investigate each frequency but to clarify each relationship. The existence of PCB with overlapping FS and BBE provides clinical evidence that PCB and these conditions form a continuous spectrum. Cases of PCB with preserved MRS were previously reported, and it was proposed that this condition could be considered GBS in a broad sense based on a common pathogenesis.<sup>25</sup> A patient with PCB with preserved MRS has been described,<sup>14</sup> and we identify 8 similar cases herein. Except for hypoflexia or areflexia in the arms, the clinical features did not differ for pure PCB and PCB with preserved MRS, supporting evidence that PCB with preserved MRS can be considered PCB. In our study, patients with PCB-like symptoms who had leg weakness were assigned the diagnosis of GBS overlap for simplicity. All patients with GBS overlap showed weakness in the pharynx, neck, and arms at an early stage that eventually spread to the legs, and limb weakness predominated in the arms during the illnesses.

Upper respiratory tract infection preceded PCB more frequently than diarrhea, but serological studies demonstrated that *C. jejuni* is the most common antecedent infec-
tious agent in PCB. Cytomegalovirus is the second most common, and a patient with PCB who had antecedent upper respiratory illness and serological evidence of this infection has been described. 

Antecedent infections did not differ between PCB and GBS. Compared with the patients with FS, the frequency of antecedent H influenzae infection in the patients with PCB was lower, and that of antecedent C jejuni infection was higher. In terms of antecedent infectious agents, PCB was closer to GBS than to FS.

Investigators have focused on monospecific anti-GT1a antibodies in PCB, 

but our findings indicate that anti-GT1a antibodies with GQ1b reactivity frequently were present. Our study also showed that 27.8% of the patients with PCB had IgG antibodies to GM1, GM1b, GD1a, or GaNAc-GD1a (serological markers of AMAN). This common immunological profile indicates that PCB is related to AMAN. Previously, 2 PCB cases associated with anti-GM1b or anti-GD1a IgG antibodies were reported, and the electrodiagnosis was AMAN.

The antecedent illness of both patients had been C jejuni enteritis. Campylobacter jejuni strains from FS and GBS express GT1a-like and GD1a-like lipo-oligosaccharides. After C jejuni infection, some patients may develop anti-GT1a or anti-GD1a IgG antibodies and PCB. The present study also showed that 39.0% of the patients with PCB who had anti-GQ1b IgG antibodies (a serological marker of FS and BBE), indicating that PCB is related to FS and BBE.

In conclusion, this large study clarifies the clinical profiles of patients with PCB. It identifies clinical overlapping, frequent C jejuni infection, and common anti-ganglioside antibodies in PCB, GBS, FS, and BBE, providing conclusive evidence that they form a continuous spectrum.

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