Indicators of rapid clinical recovery in Guillain-Barré syndrome

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Abstract
To elucidate the features of patients with Guillain-Barré syndrome who show markedly rapid clinical recovery, clinical, serological, and electrophysiological data of 80 consecutive patients were reviewed. Antigangliosides, and Campylobacter jejuni and Haemophilus influenzae antibodies were measured by enzyme linked immunosorbent assays. Nine (11%) patients showed rapid recovery (improvement by two or more Hughes grades within 2 weeks). They often had electrodagnosis of acute motor axonal neuropathy (AMAN; 67%), preserved tendon reflexes (44%), anti-GM1 antibodies (89%), preceding H influenzae infection (44%), and received immunoglobulin treatment (44%). On the other hand six patients with poor prognosis often had AMAN (100%) and anti-GM1 antibody (83%), but a higher incidence of preceding C jejuni infection (83%). It is concluded that patients with Guillain-Barré syndrome with AMAN and anti-GM1 antibodies have either faster or slower recoveries. Among the axonal subgroup of patients with Guillain-Barré syndrome, preserved tendon reflexes, H influenzae infection, and the patient having received immunoglobulin treatment may be indicators of rapid recovery.

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Guillain-Barré syndrome is a monophasic disease with spontaneous or treatment induced recovery. Several factors have been suggested as prognostic indicators in Guillain-Barré syndrome. These include age of patient, speed of progression, respiratory muscle paralysis, amplitude of distally evoked compound muscle action potential (CMAPs), the presence of anti-GM1 antibody and Campylobacter jejuni infection.2 3

Guillain-Barré syndrome is now classified into demyelinating and axonal categories according to clinical, serological, electrodiagnostic, and pathological criteria.3 4 The axonal subtype of Guillain-Barré syndrome, termed acute motor axonal neuropathy (AMAN),5 is characterised by primary axonal damage.4 Patients with AMAN invariably have low distal CMAPs, which, according to previous studies, usually indicate a poor prognosis or slow recovery. Some patients with AMAN actually experience poor outcomes,5 but a considerable number recover quickly and some of them can have an even more rapid improvement than patients with demyelinating Guillain-Barré syndrome.6

Whereas almost all previous studies have focused on factors associated with poor prognoses,7 8 we aimed to elucidate the clinical, serological, and electrophysiological features of patients with Guillain-Barré syndrome with rapid recovery. The data suggest that certain factors could be indicators of rapid recovery in Guillain-Barré syndrome.

Patients and methods
Eighty patients with Guillain-Barré syndrome, who attended Chiba University Hospital or its affiliated hospitals between 1993 and 1999, were studied. They fulfilled the clinical criteria for the disease5 except for that of areflexia. Their median age was 42 years (range 3 to 80 years). Patient disability was evaluated with the Hughes functional grading scale (grade 1, minimal symptoms and signs, able to run; grade 2, able to walk 5 m independently; grade 3, able to walk 5 m with the use of aids; grade 4, chair or bed bound; grade 5, requires assisted ventilation), and was followed for up to 6 months after the onset of disease. Rapid clinical recovery was defined as improvement by 2 or more Hughes grades within 2 weeks from the peak of the illness, whereas slow recovery was defined as inability to walk independently 6 months after onset.

Patients’ serum samples taken during the first 3 weeks after onset, before immune treatment, were frozen at –80°C and stored until use. The serum samples were tested to detect recent infection by C jejuni, Haemophilus influenzae, Mycoplasma pneumoniae, cytomegalovirus, or Epstein-Barr virus. C jejuni and H influenzae antibodies were measured by an enzyme linked immunosorbent assay (ELISA), as described elsewhere.10 11 The same serum samples were tested for the presence of IgM and IgG antibodies against gangliosides GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1b,
and GQ1b by an ELISA, as described elsewhere.10

Nerve conduction studies were done using conventional procedures within 16 days of the onset of Guillain-Barré syndrome. Patients were classified as having acute inflammatory demyelinating polyneuropathy (AIDP) or AMAN according to the electrophysiological criteria of Ho et al.12

**Results**

Nine (11%) of the 80 patients with Guillain-Barré syndrome had a rapid recovery. At the peak of the disease, their clinical disability was not significantly different from that of all patients with Guillain-Barré syndrome (table): Hughes grade 4 in five of them, 3 in three, and 2 in one. These nine patients were treated with plasmapheresis (n=5) or intravenous immunoglobulin (n=4). Their condition began to improve 2 to 6 days after the initiation of the treatment, and within 14 days, they had improved by 2 or more Hughes grades. On the other hand, six (8%) patients were unable to walk independently by the end of the study and were classified as having a slow recovery. At the peak of the disease, all six of these patients had Hughes grade 4, and 6 months after the onset of the disease, the Hughes grade remained 4 in five of them.

Table 1 shows clinical features of the subgroups of patients with Guillain-Barré syndrome with rapid recovery. The age of a patient did not increase his or her likelihood of a rapid recovery. Patients with rapid recovery often had preserved tendon reflexes (44%). Intravenous immunoglobulin (IVIg) therapy tended to be associated with rapid clinical recovery: four (44%) of the nine patients with rapid recovery were treated with IVIg. The intervals between the neurological onset and the initiation of treatment did not significantly differ between patients with rapid recovery and all patients with Guillain-Barré syndrome. Patients with slow recovery often had antecedent gastroenteritis (83%).

Table 1 also shows the relation of rapid recovery with preceding infection, anti-GM1 antibody, and electrodagnosis. Patients with rapid recovery often had preceding *H influenzae* infection: nine (11%) of 80 patients had positive serology for *H influenzae*, and they often had anti-GM1 antibody (89%), the AMAN pattern (67%), and good recovery (four patients had “rapid recovery” and the remaining five were able to walk 4 weeks after onset). Infections by *C jejuni* were not frequent (22%) in patients with rapid recovery and were significantly more frequent in patients with slow recovery (83%). Preceding infections by cytomegalovirus, *M pneumoniae*, and Epstein-Barr virus had no significant correlation with the patterns of recovery. Among anti-ganglioside antibodies, anti-GM1 IgG antibody correlated with both rapid and slow recoveries. The AMAN pattern was often found for both patient groups, with rapid (67%) and slow (67%) recovery.

**Discussion**

Our results showed that factors such as preserved tendon reflexes, preceding *H influenzae* infection, and IVIg treatment, are associated with markedly rapid recovery in Guillain-Barré syndrome. Whereas patients with rapid recovery often had anti-GM1 IgG antibodies and an AMAN electrodagnosis, these features were also frequent in patients with slow recovery. Our findings, therefore, confirmed that the axonal subtype of Guillain-Barré syndrome has different patterns of recovery from those of the classic demyelinating form of Guillain-Barré syndrome (AIDP): patients with axonal Guillain-Barré syndrome can show both rapid and slow recoveries.8

Tendon reflexes tend to be preserved in patients with acute motor axonal neuropathy and anti-GM1 antibody.13 It has been reported that some Chinese1 and Japanese13 patients with Guillain-Barré syndrome have even had exaggerated tendon reflexes in the early recovery phase, and most of these have had good recoveries. Furthermore, anti-GM1 antibodies and AMAN are occasionally associated with evidence of increased motor neuron excitability.15 In the present study, patients who, at the peak of the disease, had relatively preserved reflexes often showed rapid improvement. It is reasonable to think that patients with preserved tendon reflexes recover quickly because at least some of the motor units need to function to elicit visible reflexes: van der Meché et al.14 found that, in patients with pure motor Guillain-Barré syndrome, tendon reflexes were preserved up to MRC grade 3 paresis.

In this study, nine (11%) of 80 patients with Guillain-Barré syndrome had serological evidence of recent *H influenzae* infection. Four of the nine patients with rapid recovery had preceding *H influenzae* infection, and the remaining five patients with *H influenzae* infection did not have slow recovery. *H influenzae* is a gram negative bacillus with an outer membrane containing lipopolysaccharide. This bacteria has recently been recognised as a pathogen that can elicit axonal Guillain-Barré syndrome,11,15 and its incidence in a study of 46 patients in Japan has been reported to be 13%.11 The good recovery rate in *H influenzae* infection...
related disease was by contrast with poor outcomes in *C jejuni* related disease. Rees *et al* showed that preceding *C jejuni* infection is a marker of a poor prognosis. The reason for the different speeds of recovery in *H influenzae* and *C jejuni* related Guillain-Barré syndrome is unknown, but it is clinically relevant that recovery depends on the micro-organisms of the preceding infection.

This study showed that patients with rapid recovery were treated with IVIg more often than other patients with Guillain-Barré syndrome. Jacobs *et al* reported that, among their 31 anti-GM1 positive patients, the recovery in 21 patients treated with IVIg was significantly faster than in 10 patients treated with plasmapheresis. Our findings are consistent with the results of this study because almost all of our patients with rapid recovery contained anti-GM1 antibodies.

The very rapid clinical recovery seen in our patients suggests that, as speculated in previous studies, instead of axonal degeneration or demyelination, reversible effects such as impaired physiological nerve conduction occur on the axonal membrane. These findings further suggest that the pathophysiology in the axonal subtype of Guillain-Barré syndrome is potentially reversible, especially in the early stages, and effective treatment could result in very rapid improvements. It is concluded that axonal subtype, preserved tendon reflexes, preceding *H influenzae* infection, and the patient having received IVIg treatment could be indicators of rapid recovery in Guillain-Barré syndrome.
