

Recovery patterns and long term prognosis for axonal Guillain–Barré syndrome

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Background: Little is known about the long term prognosis for patients the severe acute motor axonal neuropathy (AMAN) form of Guillain–Barré syndrome (GBS), unlike those with acute inflammatory demyelinating neuropathy (AIDP).

Objective: To clarify the long term prognosis for patients with AMAN.

Methods: Clinical recovery and outcome in 97 consecutive GBS patients were reviewed.

Results: Electrodiagnostic criteria showed that 44 patients (45%) had AMAN, 33 (34%) had AIDP, and 20 (21%) were unclassified. Most of the severely affected patients had received plasmapheresis or immunoglobulin therapy. Slow recovery (inability to walk independently at six months after onset) was found in six of the AMAN patients (14%) and in two of the AIDP patients (6%). Of the six AMAN patients, four could walk independently one year after the onset, and the other two could walk independently at 28 and 57 months after onset. Of the two AIDP patients, one could walk at nine months after the onset while the other died of pneumonia seven months after onset.

Conclusions: AMAN electrodiagnosis is not always a marker of poor recovery. Almost all the severe AMAN patients who had slow recoveries over the first six months could eventually walk independently, although some required several years.

On the basis of pathological and electrophysiological observations, Guillain–Barré syndrome (GBS) has been regarded as a type of demyelinating neuropathy. In 1986, Feasby *et al* identified an axonal type of GBS coupled with poor recovery characterised by severe Wallerian-like degeneration in the peripheral nerves at necropsy.¹ In the 1990s, a pure motor axonal form of GBS, designated acute motor axonal neuropathy (AMAN), was recognised in northern China^{2–4} and later reported in other countries.^{5–12} Based on the electrophysiological and pathological findings, GBS is currently divided into demyelinating and axonal forms: acute inflammatory demyelinating polyneuropathy (AIDP) and AMAN.^{1–12} Axonal GBS is usually characterised by electrophysiological and pathological evidence of axonal degeneration of the motor nerves together with functional conduction failure or other pathophysiology, and a possible association with anti-ganglioside antibodies, *Campylobacter jejuni* infection, or both.¹⁰ Electrophysiological evidence of axonal degeneration is thought to be an indicator of poor prognosis,^{8 13–18} but AMAN patients often show rapid recovery.^{9 19–21} Moreover, little is known about the long term outcome in these patients. We investigated differences in recovery patterns of AIDP and AMAN patients, and clarified the long term prognosis for severely disabled AMAN patients.

METHODS

Patients

We studied a series of 97 consecutive GBS patients seen at Chiba University Hospital or Matsudo Municipal Hospital between 1992 and 2002. All fulfilled the clinical criteria for GBS.²² Disabilities were evaluated on the Hughes functional grading scale (grade 6, dead; grade 5, requires assisted respiration; grade 4, bed bound; grade 3, able to walk 5 m with aid; grade 2, ambulates independently; grade 1, minimal signs and symptoms, able to run; grade 0, normal). Patients were followed for more than six months from neurological onset. Rapid recovery was defined as an improvement by two or more Hughes grades within four weeks after onset, and

slow recovery as the inability to walk independently (grade 3 or more) six months after neurological onset.

Electrophysiology

Nerve conduction studies were undertaken using conventional procedures. Motor conduction studies were made on the median, ulnar, tibial, and peroneal nerves, and sensory conduction studies on the median, ulnar, and sural nerves. Patients were classified as having AMAN or AIDP on the basis of the electrodiagnostic criteria of Ho *et al*.⁴ When patients had one of the following findings in two or more nerves during the first two weeks of illness, they were classified as having AIDP:

- conduction velocity <90% of lower limit of normal if amplitude is >50% of the lower limit of normal; <85% if amplitude is <50% of lower limit of normal;
- distal latency >110% of upper limit of normal if amplitude is normal; >120% of upper limit of normal, if the amplitude is less than lower limit of normal;
- evidence of unequivocal temporal dispersion;
- F response latency >120% of normal.

When patients had no evidence of demyelination as defined for AIDP, and had a decrease in CMAP to <80% of lower limit of normal in two or more nerves, they were classified as having AMAN.

Statistical analysis

Differences in proportions were tested with the χ^2 or Fisher's exact test, and differences in medians with the Mann–Whitney U test. A probability (p) value of <0.05 was considered significant. Kaplan–Meier curves were used to analyse the time taken to reach Hughes grade 2 (independent locomotion).

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; GBS, Guillain–Barré syndrome

Table 1 Clinical features

Electrodiagnosis	AMAN (n = 44)	AIDP (n = 33)	p Value
Age (y) (mean (SD))	37 (18)	44 (18)	NS
Sex (M:F) (n)	26:18	20:13	NS
Antecedent infection (n (%))			
Enteritis	23 (52%)	1 (3%)	<0.001
URTI	16 (36%)	20 (61%)	0.03
Hughes grade at nadir (n (%))			
1	2 (5%)	2 (6%)	
2	16 (36%)	9 (27%)	
3	4 (9%)	7 (21%)	
4	18 (41%)	5 (15%)	
5	4 (9%)	9 (27%)	
6	0 (0%)	1 (3%)	
Median/mean (range)	3.5/3.1 (1 to 5)	3.0/3.4 (1 to 6)	NS
Treatment (n (%))			
IVIG	13 (30%)	11 (33%)	NS
Plasmapheresis	21 (48%)	14 (42%)	NS
None	10 (23%)	8 (24%)	NS

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; IVIG, intravenous immunoglobulin; URTI, upper respiratory tract infection.

RESULTS

Patients

The 97 patients were grouped as having AMAN (n = 44; 45%), AIDP (n = 33; 34%), or unclassified (n = 20; 21%). Clinical features of the patients with AMAN or AIDP are summarised in table 1. AMAN patients more often had preceding gastroenteritis than AIDP patients, but age, sex, and the frequency of immune treatments did not differ between the two groups, nor was there a significant difference in the median Hughes grade at nadir between the groups.

“Unclassified” patients had milder conduction abnormalities which did not meet the criteria of AIDP and AMAN. Clinical severity in these patients was also milder (mean Hughes grade, 3.1). We think that these cases represent milder phenotypes of each subgroup of GBS.

Clinical recovery of AMAN and AIDP patients

Table 2 shows clinical recovery in the AMAN and AIDP groups and its relation to treatment. The AMAN group had higher percentages of patients with slow recovery (unable to walk independently at six months) and of those with rapid recovery (improvement by two Hughes grades or more during the first four weeks), but the differences were not significant. All the patients who had rapid or slow recovery had received immune treatments. There were no differences in clinical recovery between patients who had intravenous immunoglobulin therapy and those who had plasmapheresis. We also analysed the time from neurological onset until improvement by one Hughes grade to evaluate the speed of recovery of the 35 AMAN and 22 AIDP patients unable to run at nadir (fig 1). The histogram in fig 1 shows the two AMAN subgroups. Nineteen AMAN patients had improvement of one grade within four weeks, whereas for the others improvement was delayed for more than one month. In contrast, for the AIDP patients, the time required for an improvement of one grade had a relatively uniform distribution. Consequently, the Kaplan–Meier curves of the probabilities of reaching Hughes grade 2 for AMAN and AIDP patients unable to walk independently at nadir were dissimilar (fig 2).

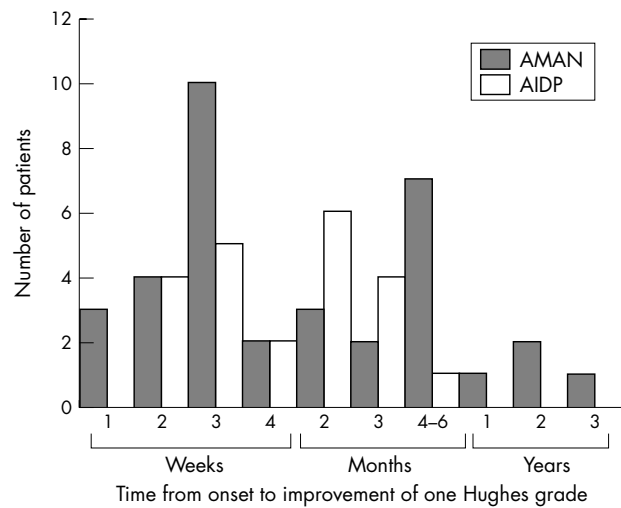


Figure 1 Histograms showing periods until an improvement of one Hughes grade from onset. The acute motor axonal neuropathy group (AMAN) (black bars; n = 35) had two subgroups of patients who improved by one grade within four weeks or over a period of months. The acute inflammatory demyelinating polyneuropathy group (AIDP) had a relatively uniform pattern (white bars; n = 22).

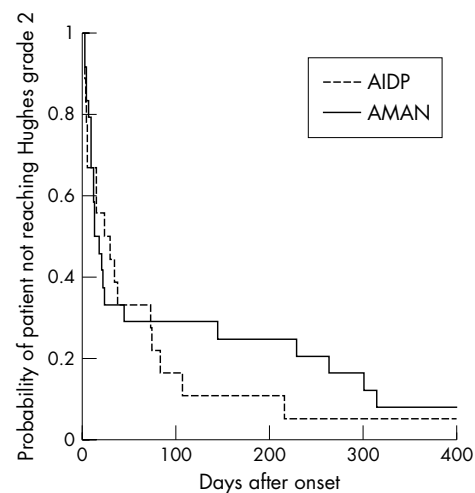


Figure 2 Kaplan–Meier curves showing the probability that patients would not recover independent locomotion (Hughes grade 2). AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy.

Patients unable to walk six months after onset

Of all the GBS patients, eight (two AIDP and six AMAN) were unable to walk (Hughes grade 3 or more) six months after onset. The clinical profiles of these eight patients are shown in table 3. All had received immune treatment. Low distal CMAP (less than 20% of the lower limit of normal) associated with a long possibly incomplete recovery, as reported previously,¹⁸ was present in six of the eight patients. Figure 3 shows the milestones in the recovery of each patient. Of the six AMAN patients, four could walk independently one year after neurological onset, one could walk independently at 28 months after the onset, and the other could walk independently at 57 months after onset. Of the two AIDP patients, one could walk independently nine months after the neurological onset, but the other died of respiratory failure and infection at seven months after the onset. No death occurred in the AMAN group.

Table 2 Recovery measures and treatment methods

Variable	AMAN			Total (n = 44)	AIDP			Total (n = 33)
	Treatment (No of patients)				Treatment (No of patients)			
	IVIG (n = 13)	PP (n = 21)	None (n = 10)		IVIG (n = 11)	PP (n = 14)	None (n = 8)	
Improvement by two or more Hughes grades during the first four weeks	4 (9%)	8 (18%)	0 (0%)	12 (27%)	4 (12%)	2 (6%)	0 (0%)	6 (18%)
Hughes grade 3 or more six months after onset	2 (5%)	4 (9%)	0 (0%)	6 (14%)	2 (6%)	0 (0%)	0 (0%)	2 (6%)

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; IVIG, intravenous immunoglobulin; PP, plasmapheresis.

DISCUSSION

Our results confirm that two patterns of clinical recovery are found in AMAN patients, in contrast to a relatively uniform recovery in AIDP patients; they showed that the long term prognosis of patients with severe AMAN was quite good, with most of the severely disabled patients being able to walk independently within a few years.

Necropsy studies of AMAN patients have detected extensive Wallerian-like degeneration in the ventral roots.³ Although some AMAN patients experience slow, incomplete recovery, many recover well.^{9 19-21} In a report on the patterns of recovery of 32 AMAN and eight AIDP patients in northern China,¹⁹ some of the AMAN group had rapid clinical recoveries, and the recovery times of AIDP and AMAN patients were similar. In our previous study of 41 GBS cases, the anti-GM1 positive patients—most of whom had AMAN—had two patterns of clinical recovery: rapid and prolonged.⁹ AMAN patients in our present study had a two phase recovery pattern similar to that of the former anti-GM1 positive patients. This good potential for recovery from AMAN suggests that extensive axonal degeneration is not always the underlying pathophysiology. The rapid recovery of AMAN patients may be explained by early resolution of physiological conduction failure at the nodes of Ranvier in the motor fibres^{19 23 24} or by collateral sprouting of surviving axons, as proposed previously.²⁰

The functional outcome of GBS in large series has been well documented.^{11 14 16 25-27} In the MGH retrospective series, 6% needed canes, crutches, or braces to walk at six to nine months, 3% remained wheelchair bound at two to three years, and 5% had died at 15 to 210 days after disease onset.²⁵ In south-east England in 1983-1984, 8% of 87 surviving GBS patients still had a disability grade of 3 or 4 one year after onset.¹⁴ At that time, 13% of the GBS patients in the study had died,¹⁴ and 20% of 79 patients in a 1993-1994 survey.²⁶ In a recent large prospective Italian study, 15% of 108 surviving GBS patients had a disability grade of 3 or more two years after onset.¹¹ In a Dutch study, 24% of 147 GBS patients had a disability grade of 2 or more at six months,¹⁶ and 11% could not walk independently 2.5-6.5 years after onset.²⁷ Immune treatment is strongly associated with the prognosis for GBS patients; thus it is hard to compare results of our present study with studies done before the introduction of intravenous immunoglobulin or plasmapheresis.

The frequency of AMAN varies according to country, from only 7% of GBS patients studied in England²⁸ and 3% in a multicentre study done in 11 Western countries²⁹ to 65% in a study in northern China.⁴ The low percentages of patients with AMAN in Western countries may affect study results. Previous studies of the long term prognosis for GBS patients in Western countries focused on AIDP, and little is known about the long term outcome for patients with AMAN. Of 32 AMAN and eight AIDP patients in northern China,¹⁹ more than 90% of the AMAN patients and all the AIDP patients could walk five metres with a walker or support. The Chinese AMAN patients, however, were markedly younger (median age 10 years) than the AIDP patients (median age 42 years). A comparison of the prognosis for AMAN and AIDP patients is therefore difficult. In the multicentre study of 369 GBS patients in 11 Western countries,²⁹ axonal GBS accounted for 3% (10 patients); 10% of those with the axonal form and 17% with the demyelinating form could not walk or were dead 48 weeks after onset. The numbers of patients unable to walk and those who died did not differ significantly for the axonal and demyelinating forms. AIDP can be accompanied by secondary axonal degeneration in severe cases, and AMAN could be associated with functional conduction block as well as axonal loss.²⁴ These might be the reasons why the long term prognosis of AMAN and AIDP is almost the same.

In our study, 8% of the 97 patients with GBS (six AMAN and two AIDP) could not walk independently at six months after onset. In the AMAN group, four of the six could walk independently one year after onset, one could walk independently 28 months after onset, and the remaining patient could walk 57 months after onset. Generally, it is believed that no further recovery can be expected two to three years after GBS,³⁰ but follow up has mainly been limited to six months or one year in most previous studies, which may be the reason for the overly pessimistic outlook for long term recovery from severe GBS.³¹ In our study, two AMAN patients who had slow recoveries could walk independently 28 and 57

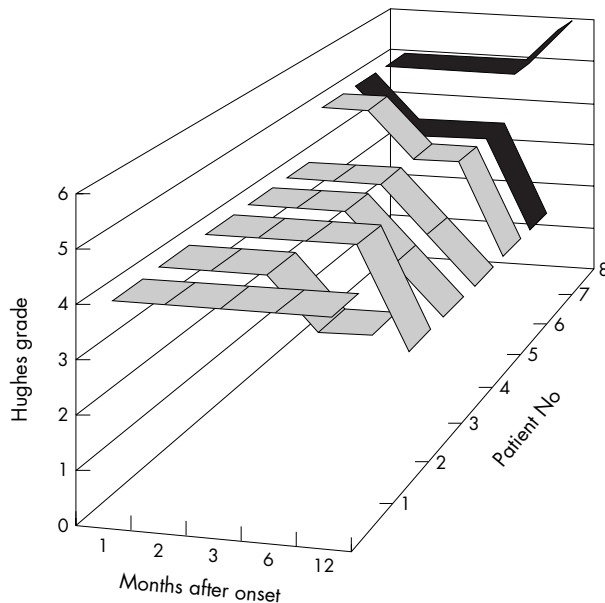


Figure 3 Milestones of recovery for Guillain-Barré syndrome patients unable to walk independently at six months after onset. Grey bars, acute motor axonal neuropathy (patients 1-6); black bars, acute inflammatory demyelinating polyneuropathy (patients 7 and 8).

Table 3 Patients unable to walk independently at six months after onset

Patient No	Age (y)	Sex	Electrodiagnosis	Antecedent infection	Treatment	Hughes grade at nadir	Days to nadir	Time (months) to reach independent locomotion	Low CMAPs*
1	43	F	AMAN	Enteritis	PP	4	15	57	Yes
2	30	M	AMAN	Enteritis	PP	5	6	28	Yes
3	44	M	AMAN	Enteritis	PP	4	1	8	No
4	17	M	AMAN	Enteritis	PP	4	7	11	Yes
5	17	M	AMAN	Enteritis	IVIG	5	7	9	Yes
6	65	F	AMAN	URTI	IVIG	5	3	10	Yes
7	53	F	AIDP	URTI	IVIG	5	9	9	Yes
8	75	F	AIDP	Others	IVIG	6	30†	–	No

*Low distal CMAPs (less than 20% of the lower limit of normal) in at least two nerves.

†Hughes grade 5 considered to be the peak of illness 30 days after onset; died (Hughes grade 6) seven months after onset.

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CMAP, compound motor action potential; F, female; IVIG, intravenous immunoglobulin; M, male; PP, plasmapheresis; URTI, upper respiratory tract infection.

months after onset. In addition, in the Dutch study, 21% of the GBS patients continued to improve after 2.5 to 6.5 years.²⁷ The mechanism of improvement in patients with severe GBS several years after onset is not clear, but axonal regeneration along the course of the nerve may account for it.

Conclusions

Most of the severely disabled AMAN patients who are unable to walk six months after onset, may still show improvement over a period of years and may ultimately be able to walk independently. Neurologists should conduct long term follow up studies of severe AMAN patients and recommend long term rehabilitation.

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