Electrophysiological Classification of Guillain-Barré Syndrome: Clinical Associations and Outcome

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We performed electrophysiological and serological testing within 15 days of symptom onset on 369 patients with Guillain-Barré Syndrome (GBS) enrolled in a trial comparing plasma exchange, intravenous immunoglobulin, and both treatments. Patients were classified into five groups by motor nerve conduction criteria; 69% were demyelinating, 3% axonal, 3% inexcitable, 2% normal, and 23% equivocal. Six of 10 (60%) patients with axonal neurophysiology had had a preceding diarrheal illness compared with 71 of 359 (20%) in other groups. Antiganglioside GM1 antibodies were present in a higher proportion of patients with axonal physiology or inexcitable nerves than other patients. The number dead or unable to walk unaided at 48 weeks was greater in the group with initially inexcitable nerves (6 of 12, 50%) compared with the rest (52 of 357, 15%), but was not significantly different between the axonal (1 of 10, 10%) and demyelinating (44 of 254, 17%) groups. Sensory action potentials and clinical sensory examination were both normal in 53 of 342 (16%) patients, and these "pure motor GBS" patients were more likely than other GBS patients to have IgG antiganglioside GM1 antibodies and to have had preceding diarrhea but had a similar outcome. The axonal group was more likely than other groups to have normal sensory action potentials. The outcomes in response to the three treatments did not differ in any subgroup (including patients with pure motor GBS or preceding diarrhea) or any neurophysiological category.

Hadden RDM, Cornblath DR, Hughes RAC, Zielasek J, Hartung H-P, Toyka KV, Swan AV, and the Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Ann Neurol 1998;44:780–788

Guillain-Barré Syndrome (GBS) is an acute peripheral neuropathy that usually follows a respiratory or intestinal infection; it reaches its nadir within 4 weeks and then the patient recovers over weeks or months. Neurophysiological[2–5] and autopsy[3,6–11] data suggest several clearly defined GBS subgroups—acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. In most cases in developed countries, the underlying pathology is demyelination (AIDP)[6,7,9] in which secondary "bystander" axonal degeneration is usually associated with a poor recovery.[12,13] Rare patients have pathological evidence of primary axonopathy with little or no inflammation or demyelination, electrically inexcitable nerves, and poor recovery.[14] Recently, it has been recognized that a primary axonal motor neuropathy is much more common in China than Europe and North America and occurs in annual epidemics in children.[2,3] Up to 65% of northern Chinese patients are classified electrophysiologically as acute motor axonal neuropathy.[4,5,15] Axonal GBS may also be more common in India[16] and Mexico (Ramos-Alvarez M, personal communication). However, in the Chinese population there is no difference in the speed of recovery between the neurophysiologically defined axonal and demyelinating subtypes.[17]

Questions still remain in Europe and North America about the proportions of patients with physiologically defined GBS subtypes, their patterns of illness and recovery, and their relationship to important features of GBS such as preceding events. This study describes the electrophysiological subtypes in a large cohort of pa-

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Received Dec 18, 1997, and in revised form Apr 22, 1998. Accepted for publication May 1, 1998.

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tients predominantly from Europe and North America participating in a treatment trial,[1] and investigates their relationship to clinical features, antiganglioside GM1 antibodies, and outcome.

Patients and Methods

Patients

The Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial has been described.[1] In the 383 patients there was no significant difference in outcome between the three treatments. Fourteen patients were excluded for the following reasons: Symptoms began more than 14 days before randomization in 2 patients; the diagnosis of GBS was incorrect in 2; neurophysiological testing was performed more than 15 days after symptom onset in 5 and not at all in 4; and 1 was lost to follow-up at 48 weeks. Three hundred sixty-nine patients were included in the analysis. We noted whether each patient described a preceding gastrointestinal illness and the presence of any abnormal signs on clinical sensory examination (objective impairment of vibration, touch, position, or pain sensation) at randomization. The main outcome measure was disability grade on a seven-point scale.[1]

Electrophysiology

Electrophysiological testing was done twice on each patient—the first within 15 days of symptom onset (mean, 7 days; SD, 4 days; range, 1–15 days) and not more than 5 days after randomization, and the second approximately 4 weeks after the first (mean, 36 days from onset; SD, 6 days; range, 22–69 days). All results refer to the first test unless specifically stated to be from the second test. Compound muscle action potential amplitude after distal (dCMAP) and proximal (pCMAP) stimulation, conduction velocity, distal latency, and F-wave latency were recorded in approximately four (mean, 3.7; SD, 1.4) motor nerves (median, ulnar, tibial, and common peroneal) and expressed as a percentage of the upper (ULN) or lower (LLN) limit of normal for the center doing the test. The assessing physician was asked to decide whether the sensory nerve action potentials at the first test were normal or abnormal according to the criteria in use at each center. Needle electromyography was not recorded in most patients and was therefore not included in the analysis.

Electrophysiological Criteria

Several sets of criteria have been devised to detect demyelination by nerve conduction studies in patients with GBS.[15,18,19] We evaluated these different criteria sets and used a slight modification of those developed by Ho and co-workers[15] (Table 1). We defined partial motor conduction block as a pCMAP/dCMAP amplitude ratio of less than 0.5 but considered this valid only if the dCMAP amplitude was greater than or equal to 20% of LLN. It is known from observations in amyotrophic lateral sclerosis[20] and axonal GBS[21] that motor nerves with very low amplitudes due to axonopathy may have prolonged distal and F-wave latencies or reduced conduction velocity. We therefore did not allow any single nerve with dCMAP amplitude of less than 10% of LLN to change the classification of a patient. We also evaluated our patients by the criteria of the Dutch GBS study group[19] to determine if the proportion classified as demyelinating depends on the set of criteria used.

Table 1. Criteria for Electrophysiological Classification[a]

1. Normal
   (All the following in all nerves tested)
   DML ≤100% ULN
   F wave present with latency ≤100% ULN
   MCV ≥100% LLN
   dCMAP ≥100% LLN
   pCMAP ≥100% LLN
   pCMAP/dCMAP ratio >0.5
2. Primary demyelinating
   (At least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and dCMAP ≥10% LLN)
   MCV <90% LLN (85% if dCMAP <50% LLN)
   DML >110% ULN (120% if dCMAP <100% LLN)
   pCMAP/dCMAP ratio <0.5 and dCMAP ≥20% LLN
   F-response latency >120% ULN
3. Primary axonal
   None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if dCMAP <10% LLN), and
   dCMAP <80% LLN in at least two nerves
4. Inexcitable
   dCMAP absent in all nerves (or present in only one nerve with dCMAP <10% LLN)
5. Equivocal
   Does not exactly fit criteria for any other group

[a]Modified from Ho and colleagues.[15]

DML = distal motor latency; ULN = upper limit of normal; MCV = motor conduction velocity; LLN = lower limit of normal; dCMAP = compound muscle action potential amplitude after distal stimulation; pCMAP = compound muscle action potential amplitude after proximal stimulation.

Antibodies to Ganglioside GM1

All serum samples were stored and transported frozen to a single laboratory (Würzburg, Germany). Antibodies to ganglioside GM1 were measured by enzyme-linked immunosorbent assay (ELISA) by a method described previously,[22] except that all samples were incubated at 4°C overnight and ganglioside GM1 was obtained from Sigma (Deisenhofen, Germany). The titer was defined as the reciprocal of the dilution of the test serum, which gave an optical density greater than 3 SD above the mean of a pool of 50 healthy blood bank control sera. A positive result was defined as a titer of 100 or more. Because the interassay and intraassay variability was about one to two titer steps, a control sample might occasionally be positive at a low titer. All positive samples were cross-checked in an independent dot blot assay.[22] Although we attempted to obtain serum from all patients, many samples were either not sent, or inadequately centrifuged, labeled or packaged during transport, so serum was analyzed from only 241 patients.

Statistical Analysis

Results were classed as significant if $p \leq 0.05$. Tables of categorical variables were analyzed for heterogeneity by the χ^2

test, using Yates' continuity correction for two-by-two tables, or Fisher's exact test if frequencies were low. Student's t test was used for comparisons between two groups of normally distributed variables. Times until walking were compared by using the log rank test. Astute software (version 1.51, DDU Software, University of Leeds, Leeds, UK) with Excel (version 5.0, Microsoft, Redmon, WA) was used for most statistical analysis, except Prism (version 2.01, GraphPad; Software Inc, San Diego, CA) was used to calculate confidence limits and SPSS for Windows (version 6.1, SPSS, Chicago, IL) for survival analysis. The GLIM package (Francis B and colleagues, 1993, Oxford University Press, Oxford, UK) was used to cross-check results and for Poisson modeling.

Results

Electrophysiological Categories and Clinical Features

At the first neurophysiological test, 69% of patients met criteria for peripheral nerve demyelination (Table 2, first column). Approximately 3% of patients were classified as axonal, 3% inexcitable, 2% normal, and 23% equivocal. A preceding diarrheal illness occurred in a significantly higher proportion of patients in the axonal category (60%) compared with other categories (20%) (Table 3). The relative risk of axonal physiology in patients with diarrhea compared with those without was 5.7 (95% confidence interval [CI], 1.6–19.7). There was a slight predominance of males in the inexcitable group and fewer males than expected in the normal and equivocal groups. The disability grade at randomization was significantly worse in the inexcitable group (mean ± SE, 4.6 ± 0.2) than the demyelinating (4.0 ± 0.03) and axonal groups (3.9 ± 0.2). There was no significant relationship between the neurophysiological category and age or the delay from symptom onset until testing (data not shown).

Table 3. Clinical Features[a] at Randomization

	n	Patients with Diarrhea n (%)	Males[b] n (%)
Demyelinating	254	46 (18)	162 (64)
Axonal	10	6 (60)	6 (60)
Inexcitable	12	4 (33)	10 (83)
Equivocal	84	20 (24)	37 (44)
Normal	9	1 (11)	4 (44)
All	369	77 (21)	219 (59)

[a]Preceding diarrheal illness and sex.
[b]2 × 5 χ^2 test for heterogeneity: $p = 0.008$.

Electrophysiological Group Changes at Second Test (A Mean of 36 Days from Onset)

Although the proportions in each electrophysiological group were similar at both tests, many individuals changed classification during the 4 weeks between tests (see Table 2). In particular, of the 10 patients initially in the axonal group, 6 (60%; 95% CI, 26–88%) were classified later as demyelinating, 3 (30%; CI, 7–65%) equivocal, and only 1 (10%; CI, 0–44%) remained in the axonal group. In a similar manner, of the initially inexcitable patients, 5 (50%; CI, 19–81%) were reclassified 4 weeks later as demyelinating and 4 remained inexcitable. Five of 9 in the original normal group became abnormal, mostly equivocal. Of the original demyelinating group, 4% (2–8%) became axonal and 5% (2–8%) inexcitable. Almost half of the equivocal group became demyelinating at the second study.

Data for individual nerves were reviewed for all 10 patients with axonal features at the first test. Of the 6 patients who changed from axonal to demyelinating, 1 had three demyelinating nerves, and 5 had two demyelinating nerves (of which one was of low amplitude [dCMAP < 10% LLN] in 3 patients, and both were of low amplitude in 1 patient). Two patients changed from axonal to equivocal because of one demyelinating nerve, of low amplitude in 1 patient. Two patients changed classification entirely because of nerves of low amplitude; that is, 1 became demyelinating owing to

Table 2. Numbers of Patients Classified in Each Group by First and Second Electrophysiological Test

First Test (Mean 7 Days from Onset)		Second Test (Mean 36 Days from Onset)					
	% (95% CI)	Demyelinating (n = 210) 66 (61–71)	Axonal (n = 12) 4 (2–7)	Inexcitable (n = 19) 6 (4–9)	Equivocal (n = 69) 22 (17–27)	Normal (n = 7) 2 (1–5)	Not Done (n = 52) —
Demyelinating (n = 254)	69 (64–74)	166	9	10	31	1	37
Axonal (n = 10)	3 (1–5)	6	1	0	3	0	0
Inexcitable (n = 12)	3 (2–6)	5	0	4	1	0	2
Equivocal (n = 84)	23 (19–27)	33	2	4	30	3	12
Normal (n = 9)	2 (1–5)	0	0	1	4	3	1

Total n for both tests was 369.

two nerves with long distal latency, and 1 became equivocal owing to one nerve with a reduced conduction velocity. However, of the eleven nerves that changed from axonal to demyelinating, seven had at least moderate amplitudes and three of these satisfied two demyelinating criteria; five nerves developed a slow conduction velocity below 78% of LLN, four a low p/dCMAP ratio below 0.46, four a long distal latency greater than 140% ULN, and one a delayed F latency (121% ULN). Eight nerves classified initially as axonal remained axonal and four became equivocal. By the Dutch criteria[19] (which require less abnormality for conduction block) 2 of our 10 initially axonal patients would be classed at the first test as demyelinating, but only 5 of our initially axonal patients would be classed at the second test as demyelinating. In summary, the patients who changed from axonal to demyelinating were not just borderline, but rather had acquired features of demyelination as marked as in patients classed from the start as demyelinating.

Effects of Using Differing Criteria for Demyelination

Because electrophysiological criteria to define the demyelinating (AIDP) form of GBS are not uniformly agreed on, we analyzed our data by two different sets of criteria. At the first test, 56% of our patients had demyelination (AIDP) by the criteria of the Dutch group[19] compared with 69% by our own criteria.

Antiganglioside GM1 Antibodies

The axonal and inexcitable groups were more likely than other groups to have antiganglioside GM1 antibodies of immunoglobulin (Ig) classes IgM, IgG, and IgA (Table 4). IgM antibodies were present in 83% of the axonal group and 56% of the inexcitable group compared with 16% of the demyelinating group. The relative risks of axonal physiology in patients with antiganglioside GM1 antibodies compared with those without were 20.1 (95% CI, 2.4–168.2) for IgM, 17.3 (95% CI, 2.1–145.1) for IgG, and 5.7 (95% CI, 1.2–27.1) for IgA. Allowing for confounding among the three classes, only IgM had a significant independent association with electrophysiological type (Poisson regression modeling). The proportion of patients initially classified as demyelinating who later changed to axonal was significantly higher in those with IgG antiganglioside GM1 antibodies (5 of 27, 19%) compared with those without these antibodies (1 of 108, 1%; $p = 0.0006$), but there was no such relationship with IgM or IgA antibodies. Patients with antiganglioside GM1 antibodies had significantly smaller mean dCMAP amplitudes than those without antibodies: the mean (SE) dCMAP in patients with IgA antibodies was 0.47 (0.07) times the lower limit of normal, 0.67 (0.09) for IgG, and 0.81 (0.14) for IgM, compared with 1.18 (0.08) in those without antibodies of any class.

Outcomes

The time from randomization until first able to walk and the proportions unable to walk unaided at 48 weeks varied significantly among electrophysiological groups, being similar between the axonal and demyelinating groups, but markedly worse in the group with inexcitable nerves (Table 5). Ten percent (95% CI, 0–44%) of the axonal group and 17% (95% CI, 13–23%) of the demyelinating group could not walk unaided at 48 weeks, compared with 50% (95% CI, 21–79%) of the inexcitable group. The changes in disability grades between randomization and 4 weeks later did not differ significantly between groups, although the inexcitable group improved less (mean ± SE, 0.5 ± 0.3) than the demyelinating (mean ± SE, 0.9 ± 0.1) and axonal (mean ± SE, 0.8 ± 0.3) groups. The numbers of deaths by 48 weeks were not significantly different among groups.

At the second test, patients classified in the axonal group had a markedly worse outcome (5 of 12 [42%; 95% CI, 15–72%]) could not walk unaided at 48 weeks) than those in the demyelinating group (21 of 210 [10%; CI, 6–15%] unable to walk), in contrast to the lack of a difference at the first test (Table 6). However, those with inexcitable nerves at the second test retained the worst prognosis (12 of 19 [63%, CI, 38–84%] unable to walk).

Table 4. Patients with Antiganglioside GM1 Antibodies at Randomization

		GM1 IgM–Positive	GM1 IgG–Positive	GM1 IgA–Positive
	n	n (%)	n (%)	n (%)
Demyelinating	154	25 (16)	29 (19)	19 (12)
Axonal[a]	6	5 (83)	5 (83)	3 (50)
Inexcitable	9	5 (56)	6 (67)	5 (56)
Equivocal	64	12 (19)	13 (20)	9 (14)
Normal	8	1 (13)	1 (13)	0 (0)
All	241	48 (20)	54 (22)	36 (15)

[a]Axonal versus demyelinating: $p = 0.0009$ (IgM); $p = 0.002$ (IgG); $p = 0.03$ (IgA).

Table 5. Outcomes by Classification at First Electrophysiological Test

First Electrophysiology	n	Days until Walking Unaided[a]	Patients Not Walking or Dead at 48 Weeks, n (%)
Demyelinating	254	50 (21–146)	44 (17)
Axonal	10	41 (22–235)	1 (10)
Inexcitable	12	326 (22 to >336)[b]	6 (50)[c]
Equivocal	84	23 (12–76)	6 (7)
Normal	9	17 (9–65)	1 (11)
All	369	43 (18–139)	58 (16)

[a]Data are median (interquartile range) values.
[b]Inexcitable versus demyelinating: $p = 0.02$.
[c]Relative risk of not walking at 48 weeks if classified inexcitable = 3.4 (95% CI, 1.8–6.4), $p = 0.004$.

CI = confidence interval.

Table 6. Outcome by Classification at Second Electrophysiological Test[a]

Second Electrophysiology	n	Not Walking or Dead at 48 Weeks, n (%)
Demyelinating	210	21 (10)
Axonal	12	5 (42)
Inexcitable	19	12 (63)
Equivocal	69	7 (10)
Normal	7	0 (0)
All	317	45 (14)

[a]Tested at a mean of 36 days from onset.

2×5 χ^2 test for heterogeneity: $p < 0.0001$, with axonal and inexcitable groups, by far, the worst.

Mean Distal CMAP Amplitude

Poor outcome was predicted by a low mean dCMAP amplitude (≤20% of the lower limit of normal, averaged over all nerves tested in 1 patient), and more strongly at the second than the first test. Fourteen of 57 (25%) with low dCMAP at the first test could not walk unaided 48 weeks after randomization, compared with 44 of 312 (14%) with higher dCMAP. Twenty-nine of 76 (38%) with low dCMAP at the second test could not walk unaided at 48 weeks, compared with 16 of 237 (7%) with higher dCMAP. Therefore, a mean dCMAP of 20% or less of LLN predicted inability to walk at 48 weeks, with 24% sensitivity and 86% specificity at the first test, compared with 64% sensitivity and 82% specificity at the second test.

Pure Motor GBS

Fifty-three of 342 (16%) patients had both normal clinical sensory examination and normal sensory action potentials at randomization, which we have defined as "pure motor GBS." We ignored any sensory symptoms. Patients in the axonal group were significantly more likely to have pure motor GBS than those in the demyelinating group (Table 7), and the relative risk of pure motor GBS in the axonal group compared with other groups was 3.5 (95% CI, 1.8–6.8). Pure motor GBS patients were significantly more likely than other GBS patients to have had preceding diarrhea (see Table 7). The relative risk of pure motor GBS in those with diarrhea compared with those without was 2.3 (95% CI, 1.4–3.8). Pure motor GBS patients were significantly more likely than other GBS patients to have antiganglioside GM1 antibodies of the IgG class, but there was no association with the IgA or IgM classes. IgG antiganglioside GM1 antibodies were present in 19 of 41 (46%) pure motor GBS patients compared with 32 of 186 (17%) other GBS patients. The proportions dead or with poor outcome did not differ significantly between pure motor GBS patients and other GBS patients. Eleven of 53 (21%) pure motor GBS patients could not walk unaided at 48 weeks compared with 41 of 289 (14%) others ($p = 0.3$). All the above relationships were also true for the group of all patients with normal sensory action potentials, and the group with normal clinical sensory examination considered independently, except that patients with normal clinical sensory examination were more likely to have IgA antiganglioside GM1 antibodies but had no relationship with the electrophysiological group. Half (5 of 10) of the axonal group had pure motor GBS, whereas the other half (5 of 10) had sensory abnormalities on at least two of the three types of measurement (symptoms, clinical examination, and electrophysiology). Axonal groups with and without sensory abnormality did not differ significantly on any measure, including disability grade at any time, days until walking, age, presence of antiganglioside GM1 antibodies, or dCMAP amplitude.

Treatment

There was no marked difference in disability grade at 48 weeks between the three treatments within various

Table 7. Pure Motor GBS[a]

	n	Pure Motor GBS, n (%)
Demyelinating	237	27 (11)
Axonal	10	5 (50)
Inexcitable	12	1 (8)
Equivocal	75	18 (24)
Normal	8	2 (25)
All	342	53 (16)
No diarrhea	271	33 (12)
Diarrhea	71	20 (28)

[a]Defined as both sensory examination and sensory action potentials being normal.

GBS = Guillain-Barré syndrome.

subgroups such as patients with preceding diarrhea,[1] pure motor GBS, and those with normal clinical sensory examination with and without diarrhea. Of patients with normal clinical sensory examination, 8 of 38 (21%) treated with immunoglobulin could not walk unaided 48 weeks later, compared with 7 of 27 (26%) treated with plasma exchange ($p = 0.9$), and the time until first able to walk did not differ between the two treatments ($p = 0.6$). There was no evidence of a difference between the effects of the three treatments within electrophysiological groups, although numbers were too small and allocation of treatment within groups too irregular to allow any firm conclusions (data not shown).

Discussion

Electrodiagnostic Results at the First Test

Our results confirm previous studies showing that most GBS patients in North America,[18,23] western Europe,[19,24,25] and Australia[26] meet neurophysiological criteria for demyelination. It is of particular interest that use of two different sets of criteria gave similar results in our population. The Dutch criteria for demyelination[19] were met by 60% of their patients and 56% of our patients, compared with 69% of our patients demyelinating by our criteria. The Dutch criteria include CMAP duration that we did not record. Outcomes of our patients meeting their criteria did not differ significantly from our own axonal or demyelinating groups, nor from those who were demyelinating by our criteria but not by the Dutch. We conclude there is no important pathophysiological difference between the Dutch criteria for demyelination and our own. The various sets of criteria used in North America and Western Europe have suggested that 56 to 87% of GBS patients have AIDP.[18,19,24,25,27] In the absence of any gold standard diagnostic test, we cannot know which set is the most valid, so we can only rank them as "more liberal" or "more conservative." Stricter criteria designed to detect demyelination in chronic inflammatory demyelinating polyneuropathy[28] are inappropriate when used in GBS, as the proportion of GBS patients that meets chronic inflammatory demyelinating polyneuropathy criteria is much lower.[29]

We found few patients who met our criteria for axonal neurophysiology. This contrasts with results from northern China, where a much higher proportion (65%) of patients had axonal physiology compared with only 24% demyelinating.[15] The fact that we used almost identical criteria to the Chinese study implies that the criteria are not the primary reason for the geographical differences, as was previously suggested. Indeed there are similarities between the axonal groups in both locations; ie, of the Chinese patients with axonal neurophysiology, 90% have pure motor GBS, 76% have anti-*Campylobacter jejuni* antibodies, and 48% have IgG antiganglioside GM1 antibodies,[15] similar to the 10 (3%) patients in our axonal group of whom 50% had pure motor GBS, 60% had diarrhea, and 83% had IgG antiganglioside GM1 antibodies. Because *Campylobacter* infection may more often lead to axonal GBS,[15,24,30] the explanation may be simply that *Campylobacter* infection is a more frequent antecedent event in GBS in China. The Chinese cases occur predominantly in children in summer epidemics, whereas our cases appeared sporadic. There may be additional host factors that have not yet been investigated.

Other European studies have estimated the incidence of axonal GBS by using different electrophysiological criteria. Rees and colleagues,[24] in England, classified 7% of patients as axonal, according to criteria that required needle electromyography. The Italian study[25] classified 29% of patients as axonal GBS but included some that we would classify as inexcitable, demyelinating, or equivocal. The time of testing is not stated in these studies but may have been later than in ours, thus confusing primary and secondary axonopathy, attributing axonal neurophysiology to a higher proportion of patients and contributing to a worse outcome. The Dutch group has not defined criteria for axonal GBS.

Electrodiagnosis and Other Clinical Factors

Our classification of patients by motor nerve conduction studies has given useful insights into associations with other clinical features. Patients with axonal GBS were more likely than others to have diarrhea (see Table 3) and antiganglioside GM1 antibodies (see Table 4), and *Campylobacter* may be the common link.[15,24,30] There was no significant difference in outcome between the axonal and demyelinating groups. Patients with inexcitable nerves recovered more slowly than others, as previously shown, suggesting that many have undergone either primary or secondary axonal degeneration.

What Do these Electrical Groups Represent Pathophysiologically?

We cannot know what the pathological correlate of our electrophysiologically axonal patients is without biopsy or autopsy specimens, and we do not pretend they all have pure axonopathy. They are probably heterogeneous, but we feel this is less important than the fact that our classification predicts significant associations with antiganglioside GM1 antibodies, diarrhea, and pure motor GBS. Our "axonal" group may include patients with degeneration of only the most distal few millimeters of the intramuscular nerve terminal, which can rapidly regrow,[31] physiological impairment of axonal conduction due to ion channel blockage by reversible binding of antibodies or other soluble molecules with or without structural damage,[11,17,32–34] or distal demyelination with conduction block. Standard au-

topsy may fail to show any abnormality in these situations unless the whole length of nerve is examined, and standard nerve biopsy does not show pathology of motor nerves. Patients that come to autopsy are a biased selection of severe cases that are more likely to have Wallerian-like axonal degeneration.

Our inexcitable group may represent either axonopathy or severe demyelination with distal conduction block, which are electrically indistinguishable.[35–37] Our electrophysiologically normal group is probably also heterogeneous. The equivocal group includes patients with nerves of mixed types and with very mild abnormalities. We have no way of detecting coexisting axonopathy in a patient with definite features of demyelination but expect some patients have overlapping pathology.

Electrodiagnostic Group Changes between First and Second Tests

We reassessed the electrophysiological categories of patients at a second time about 5 weeks after onset (see Table 2). Some changes have simple explanations. Nerves severely affected by primary demyelination may undergo Wallerian-like degeneration so that they are in the axonal group 4 weeks later. However, it is difficult to explain the high proportion of those initially classified as axonal who later appeared demyelinating. Possible explanations include autoimmune attack on epitopes present on both axon and myelin, and conduction block or slowing due to disruption of myelin or ion channels in nerve fibers of different sizes, or to the short internodes of regenerated fibers after distal axonal damage. The distinction between axonal and demyelinating GBS may not be as fundamental as many believe. Experimental autoimmune neuritis in rats may have demyelinating or axonal pathology depending only on whether a low or high dose, respectively, of the same antigen is given.[38,39] Unfortunately, very few longitudinal data on the electrophysiology of axonal GBS have been published, so serial studies in this model would be particularly interesting.

Pure Motor GBS

We reproduced the findings from the Dutch study showing a greater proportion of patients without sensory loss having a preceding gastrointestinal illness (see Table 7) and antiganglioside GM1 antibodies.[40,41] The Dutch motor GBS group is most similar in definition to our group with no abnormal signs on clinical sensory examination. We did not reproduce their finding that patients with motor GBS had "little or no evidence of demyelination" as most of our pure motor GBS patients satisfied our criteria for demyelination (see Table 7). The proportion of pure motor GBS patients in our demyelinating group was, however, lower than in the axonal group. We found no difference in outcome in pure motor GBS patients between different treatments. This does not confirm the conclusion of the Dutch study that intravenous immunoglobulin is more effective than plasma exchange in motor GBS.[40]

Antiganglioside GM1 Antibodies

We confirm previous findings that antiganglioside GM1 antibodies are more common in pure motor GBS[40] and those with diarrhea,[42] and now show they are more common in the axonal and inexcitable groups (see Table 4), suggesting similar immunopathology between these two groups. We found antiganglioside GM1 antibodies to be twice as prevalent as in the Dutch study.[41] We confirmed their findings that patients with these antibodies had smaller mean dCMAPs and were more likely to have inexcitable nerves (motor nerves were inexcitable in 10 to 14% of our patients with these antibodies, compared with 2% without antibodies; see Table 4) and that IgG antibodies were more common in motor GBS than other GBS patients.[40] IgG antiganglioside GM1 antibodies were more common in all Chinese GBS patients than controls (42% vs 6%) but not significantly different between axonal and demyelinating groups.[15] IgM antiganglioside GM1 antibodies were not found in any Chinese GBS patient.

Antiganglioside GM1 antibodies are common in several chronic diseases of peripheral motor nerves in which they usually belong to the IgM class, whereas it is the IgG class that is usually associated with GBS[41–44] and IgG bound to the axolemma has been found in acute motor axonal neuropathy.[11] The cross-reaction of antiganglioside GM1 antibodies with the lipopolysaccharide of certain strains of *Campylobacter* is an attractive hypothesis for the etiology of some cases of GBS,[44–48] although most cases have not had preceding *Campylobacter* enteritis. The fact that antiganglioside GM1 antibodies are found in both the demyelinating and axonal groups probably indicates some overlap in the pathogenesis. We do not know whether the antibodies are the cause or the effect of the disease, and ganglioside GM1 epitopes are present on both myelin and axonal membranes.[49,50] Not all antiganglioside GM1 antibodies have the same specificity, as is shown by the differing cross-reactivity with other ganglioside epitopes, and we have yet to discover which is the most relevant specificity.

Conclusion

Categorizing European and North American GBS patients by electrophysiological parameters soon after onset identifies features of demyelination in most patients, but a few have axonopathy. Patients with axonal physiology are more likely to have had a preceding diarrheal illness and to have antiganglioside GM1 antibodies. This group does not have a significantly worse

prognosis than the group with electrophysiological features of demyelination. A second neurophysiological study 4 to 6 weeks after onset predicts the long-term prognosis more accurately than the initial study. In pure motor GBS, electrophysiological axonopathy is more common, and preceding diarrhea and the presence of IgG antiganglioside GM1 antibodies are more likely. None of the electrophysiological groups, nor groups defined by preceding diarrhea or pure motor GBS, predicts a significant differential response to intravenous immunoglobulin, plasma exchange, or combined treatment.

Appendix: Clinical Neurophysiologists

Neurophysiological studies were performed by the following, in addition to the principal investigators listed in Reference 1: L. Davies (Sydney, Australia); A. Brunen, P. Theys, and E. Peeters (Leuven, Belgium); F. Wang (Liège, Belgium); D. W. Zochodne (Calgary, Canada); C. F. Bolton (London, Ontario, Canada); K. Kong (Toronto, Ontario, Canada); E. Hund and V. Schuchardt (Heidelberg, Germany); S. Merkelbach (Homburg/Saar, Germany); J. Schwarz (Munich, Germany); K. Reiners (Würzburg, Germany); Z. Argov (Jerusalem, Israel); L. Marzorati (Monza, Italy); T. Sand (Trondheim, Norway); M. R. Alves and M. de Carvalho (Lisbon, Portugal); J. Heath (Cardiff, UK); R. E. Cull (Edinburgh, UK); A. C. Mann (Glasgow, UK); B. M. Tedman (Liverpool, UK); N. M. F. Murray, J. Payan (London, UK); R. C. Marshall (Middlesbrough, UK); K. R. Mills and R. P. Kennett (Oxford, UK); R. J. van der Star (Southampton, UK); D. H. Weinberg and M. T. Hayes (Boston, MA); and J. K. Baruah (Milwaukee, WI).

We are grateful for financial support from Novartis, from the BIOMED Inflammatory Neuropathy Cause and Treatment Programme for Dr Hadden, from the Hertie Foundation and Würzburg University Research Funds for Drs Zielasek, Hartung, and Toyka, and from the James P. Dunn and Donald and Rosalie Dietz Neuromuscular Funds for Dr Cornblath. We thank H. Klüpfel, M. Piepenschneider, and K. Zehe for expert technical assistance in the determination of antiganglioside antibodies.

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