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The prognosis and main prognostic indicators of Guillain–Barré syndrome

A multicentre prospective study of 297 patients

The Italian Guillain–Barré Study Group*

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Summary

To assess the prognosis of the Guillain–Barré syndrome and identify the main prognostic indicators, 297 patients with Guillain–Barré syndrome recruited through a network of Italian centres were followed up for 24 months or until clinical recovery, whichever was earliest. For each patient the time to plateau, improvement, clinical recovery, or death was calculated, and prognostic indicators (age, sex, antecedent events, disability at admission and nadir, electrophysiological patterns) and treatments were noted. The mean duration of follow-up was 309 days. During this period, 212 patients (71%) recovered, 48 (16%) had residua and 33 (11%) died. The mean times to nadir, improvement and clinical recovery were 12, 28 and 200 days. Using life-tables and survival curves, the cumulative probability of achieving the plateau of symptoms was 73% by 1 week and 98% by 4 weeks. Improvement started during the first week in 36% of cases and within 4 weeks in 85%. The rates of clinical recovery at 1 and 4 weeks, 6, 12 and 24 months were 4, 24, 57, 70 and 82%, respectively. The chance of recovery was significantly affected by age, antecedent gastroenteritis, disability, electrophysiological signs of axonopathy, latency to nadir and duration of active disease. The main treatments did not seem to affect the chance of recovery.

Keywords: Guillain–Barré syndrome; acute polyneuritis; prognosis; prognostic factor

Introduction

Guillain–Barré syndrome was understood, until recently, to be an acute or subacute demyelinating inflammatory polyradiculoneuropathy with a favourable outcome and complete recovery in the majority of individuals (Ropper *et al.*, 1991). This rather optimistic view has been recently challenged by reports of several cases with a more severe course, presenting greater disability during the acute phase of the disease and persistent residua in the follow-up. In these cases an antecedent *Campylobacter* enteritis, axonal damage and a positive response to anti-GM1 antibodies were frequent findings (Feasby *et al.*, 1986; Yuki *et al.*, 1990; McKhann *et al.*, 1993; Griffin *et al.*, 1995; Hoe *et al.*,

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1995). These reports support the concept that Guillain–Barré syndrome is a heterogeneous symptom complex, of which inflammatory polyradiculoneuropathy is one cause and acute axonal neuropathy another (Thomas, 1992), and that the outcome of the disease is sometimes unfavourable and can be predicted by the presence of selected prognostic indicators.

There are few useful reports in the literature on the natural history of the disease, as Guillain–Barré syndrome is a rare condition (incidence rate 1–2 cases per 100 000 population per year) (Alter, 1990) and studies in the largest sample populations tended to recruit patients with more severe disease varieties who were enrolled as controls in clinical trials (Guillain–Barré Syndrome Study Group, 1985; French Cooperative Group, 1987; van der Meché *et al.*, 1992; Guillain–Barré Syndrome Steroid Trial Group, 1993) or had only a short follow-up (up to 1 year) (Ravn, 1967; Samantray *et al.*, 1977; Winer *et al.*, 1988) or were retrospective (Raphael *et al.*, 1986). In addition, many effective therapeutic strategies have been developed in the last few years, and may have affected the short-term and possibly even the long-term course of the disease (French Cooperative Group, 1992).

A large and fairly representative sample of patients with Guillain–Barré syndrome followed for a prolonged period, with a standard definition of the diagnosis and clinical characteristics of the disease and constant monitoring of treatments would be the ideal target population for a study on the prognosis of Guillain–Barré syndrome. A multicentre prospective study on a large inception cohort of patients with newly diagnosed Guillain–Barré syndrome has been recently completed in Italy. The aims of this study were (i) to define the basic steps in the prognosis of the disease after prolonged observation, and (ii) to identify the main prognostic indicators.

Material and methods

Starting on April 14, 1988 and ending on December 31, 1993, all patients with a diagnosis of typical Guillain–Barré syndrome were recruited through a large network of Italian centres. The study population comprised 247 patients from 14 university and hospital departments (Northern Italy, eight; Central Italy, two; Southern Italy, four) and 50 patients from 19 university and hospital centres enrolled in 1992 during an incidence study of Guillain–Barré syndrome in Emilia-Romagna, a Northern Italian region with a population of 2 000 000.

The diagnosis of Guillain–Barré syndrome, following a slightly modified version of the diagnostic criteria of the National Institutes of Neurological and Communicative Disorders and Stroke Committee (1978) was made in the presence of progressive bilateral muscle weakness with tendon areflexia or severe hyporeflexia, absence of sharp sensory level and absence of conditions known to cause acute polyneuropathy. A patient was excluded in the presence of at least one of the following: (i) marked, persistent asymmetry of the neurological signs; (ii) >50 mononuclear leucocytes in the spinal fluid; (iii) conditions such as diabetic or alcohol neuropathy, neuropathies associated with industrial agents, metals and drugs, poliomyelitis, and porphyria.

Ad hoc questionnaires were used to collect the main demographic variables, clinical history, neurological and laboratory findings, and details of treatment. Each eligible patient was required to be assessed on the date of hospital admission, after 1 and 2 weeks, 1, 2, 6, 12 and 24 months, or until complete clinical recovery, whichever was earliest. Clinical recovery was defined as absence of symptoms and signs potentially interfering with the daily living activities.

At each visit, a complete neurological examination was performed, and the severity of the clinical findings, which was left to the judgement of the attending physician, was expressed with reference to a disability scale commonly used in previous therapeutic trials of plasma exchange (Hughes *et al.*, 1978). The major steps in the outcome of the disease (plateau, improvement, clinical recovery or death) were carefully noted and their dates recorded. The main prognostic indicators were expressed with reference to previously identified categories or to standard definitions. Selected age groups (<15 years; 15–34 years; 35–54 years; 55+ years) were used to separate patients into meaningful prognostic groups. Antecedent events were carefully recorded with reference to a detailed check list. Included were common and unusual events, and drug exposures, in the 4 weeks preceding the onset of the neurological symptoms. Electrophysiological examination was done in accordance with standard procedures, which were precisely indicated in the questionnaire. In patients with more than one examination, only the first report was considered. For each examination, the electrophysiological pattern was expressed as normal, demyelinating, axonal or mixed. The criteria for demyelination used in the present study are a slightly modified version of the research criteria reported by the Task Force for chronic inflammatory demyelinating polyneuropathy (Ad Hoc Subcommittee of the American Academy of Neurology, 1991) and the criteria for primary axonopathy are those of Yuki and Miyatake (1993) (Table 1).

All the examinations done in detail were centrally evaluated by a commission of experts, who expressed a blind judgement. A consensus was required on examinations which gave rise to contradictory judgements. Although the treatments were left to the physicians' discretion, drug treatments had to be specified in detail (drug, daily dosage, treatment schedule and duration). Details of plasma exchange (number of exchanges, plasma volume removed, type of replacement fluids, venous access, etc.) were noted separately. Adverse treatment events were recorded and related to *ad hoc* check-lists.

The data were processed using the Statistical Package for the Social Sciences (1995). For every prognostic factor univariate analysis was done using the χ^2 test, Student's t test, and analysis of variance, where indicated. Variables subject to the length of follow-up (plateau, improvement, clinical recovery and death) were analysed using actuarial methods and plotted as separate curves. Time to clinical recovery was then selected as the major end-point of the

Table 1 *Prognosis of Guillain–Barré syndrome in Italy: electrodiagnostic criteria used in the study*

Criteria for demyelination include at least two of the following*:
(1) Conduction velocity <80% of lower limit of normal if amplitude exceeds 80% of lower limit of normal; <70% if amplitude is <80% of lower limit of normal (two or more motor nerves).
(2) Distal latency exceeding 125% of upper limit of normal if amplitude is >80% of lower limit of normal; >150% if amplitude is <80% of lower limit of normal (two or more motor nerves).
(3) *F*-response absent or latency exceeding 120% of upper limit of normal if amplitude is >80% of lower limit of normal; >150% if amplitude is <80% of lower limit of normal (two or more motor nerves).
(4) Partial conduction block or increase in duration or temporal dispersion of the CMAP (one or more motor nerves): either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.

Criteria for primary axonopathy include the following†:
(1) Inexcitable or markedly reduced‡ CMAP (two or more motor nerves).
(2) Absence of electrophysiological findings suggesting demyelination, including absence of distal conduction block.

Criteria for mixed neuropathy include the following:
(1) Inexcitable or markedly reduced CMAP (two or more nerves).
(2) Presence of at least two electrophysiological findings suggesting demyelination.

CMAP = compound muscle action potential. *Slightly modified from Jiang *et al.* (1995); †slightly modified from Kaur *et al.* (1986); ‡values exceeding 2.5 SD from the means for the controls.

Table 2 *Prognosis of Guillain–Barré syndrome in Italy: general characteristics of the sample*

Variable	No. of cases	%
Total	297	100.0
Sex		
Male	193	65.0
Female	104	35.0
Age (years)		
<15	16	5.4
15–34	71	23.9
35–54	71	23.9
>54	139	46.8
Antecedent events†		
Influenza	78	26.3
Upper respiratory infection	45	15.2
Gastroenteritis	26	8.8
Other	32	10.8
None	116	39.1
Disability at hospital admission*		
Mild symptoms/signs	32	10.8
Unassisted gait (5 m)	40	13.5
Assisted gait (5 m)	67	22.6
Chair/bedbound	116	39.1
Assisted ventilation	42	14.1
Disability at maximum worsening*		
Mild symptoms/signs	29	9.8
Unassisted gait (5 m)	40	13.5
Assisted gait (5 m)	58	19.5
Chair/bedbound	115	38.7
Assisted ventilation	55	18.5
Electrodiagnostic features‡		
Demyelinating	10	10.7
Axonal	27	29.0
Mixed	42	45.2
Normal	14	15.1

Included are 93 patients with complete records evaluated by an *ad hoc* commission. *See Hughes *et al.* (1978); †events reported in the 4 weeks preceding onset of neurological symptoms; 'other' included unspecified fever (eight cases), *Herpes zoster* (six), immunization (five) and surgery (four); ‡*see* Table 1 and text.

study. Life tables and survival curves were constructed for the whole cohort and in subsamples, according to the main prognostic indicators. Patients who died were retained and censored at the time of death. Statistical significance was estimated with the log rank test (Peto *et al.*, 1977). Multivariate analysis of the risk factors was conducted using Cox's proportional hazard function (Cox, 1972) adjusting for treatment(s) and centre.

Results

During the study period, a total of 297 patients fulfilled the criteria required for inclusion. Except for 10 patients who were recruited in hospital haematology departments, all the others were all from neurology units. Their general characteristics are illustrated in Table 2. The sample comprised 193 men and 104 women aged 3–87 years. An antecedent event was reported in 181 cases (61%). The commonest illness preceding the onset of neuritic symptoms was influenza, followed by upper respiratory infection and gastroenteritis. Less frequent antecedents were fever (eight cases), *Herpes zoster* (six cases), immunization (five cases) and surgery (four cases). Four patients had received influenza vaccine and one diphtheria/pertussis/tetanus vaccine. At hospital admission 11% of patients had mild to moderate symptoms while 39% were chair- or bedbound and 14% had respiratory insufficiency. The percentage of patients with respiratory failure seemed to increase with age (<35 years, 7%; 35–54 years, 13%; 55+ years, 18%)

The patients were followed for a mean (SEM) period of 309 (20) days. Evaluation was incomplete for 32 patients (10%) (i.e. survivors not achieving clinical recovery when last follow-up was <24 months). Of these, 15 had been examined for <6 months, five for 6 to 12 months, and 12 for 1 year or longer. Thirty-three patients (11%) died before clinical recovery (Table 3).

In seven of these, neuritic symptoms had shown some improvement before death. Cardiac arrest in the context of a dysautonomic syndrome was the leading cause of death. Sixteen cases died during the first 30 days and 21 during the first 2 months. Patients who died were older (26 were 58

Table 3 *Prognosis of Guillain–Barré syndrome in Italy: list of patients who died (total 33) with cause and interval from onset of symptoms to death*

Interval (days)	No. of cases	Cause(s) of death	No. of cases
<7	8	Dysautonomic syndrome with cardiac arrest	6
		Shock	1
		Cardiac arrest	1
7–30	8	Dysautonomic syndrome	1
		Massive intestinal infarction	1
		Respiratory infection	1
		Stroke	1
		Pulmonary embolism	1
		Cardiorespiratory failure	1
		Respiratory failure NOS	1
		Infection NOS with fever	1
31–60	5	Pulmonary embolism	1
		Cardiac arrest	1
		Pneumonia and cardiac arrest	1
		Cardiorespiratory failure	1
		Respiratory failure NOS	1
61–90	5	Pneumonia	1
		Myocardial infarction with pericarditis, hepatic cyrrhosis and pneumonia	1
		Cardiac arrest and dilated myocardiopathy	1
		Glioblastoma	1
		Acute renal failure	1
91–210	4	Cardiorespiratory failure 1	
		Colon cancer	1
		Septicemia	1
		Lung cancer	1
211–360	1	Cardiac arrest and autoimmune anemia	1
>360	1	Myocardial infarction	1

NOS = not otherwise specific.

years or older), with moderate to severe Guillain–Barré syndrome at entry (bedbound 11; respiratory failure 17). Influenza was the antecedent illness in eight cases, gastroenteritis in three and upper respiratory infection in one. Axonopathy was the commonest electrophysiological feature (five cases) followed by combined axon and myelin impairment (four cases). However, the distribution of the antecedents and the electrophysiological features of patients who died was similar to that of survivors.

The mean (SEM) time to the nadir of symptoms was 12 (1) days. The times to improvement and clinical recovery were 28 (2) and 200 (15) days. At last follow-up 48 patients (16%) were reported to have residua and 212 (71%) to have recovered. The cumulative probability of achieving the plateau of symptoms was 73% by 1 week, 84, 89 and 98% by 2, 3 and 4 weeks, respectively (Fig. 1). Improvement of symptoms started during the first week in 36% of cases, the second week in 56%, the third and fourth week in 67% and 85% of cases.

The rate of clinical recovery was slower, as at 1 week

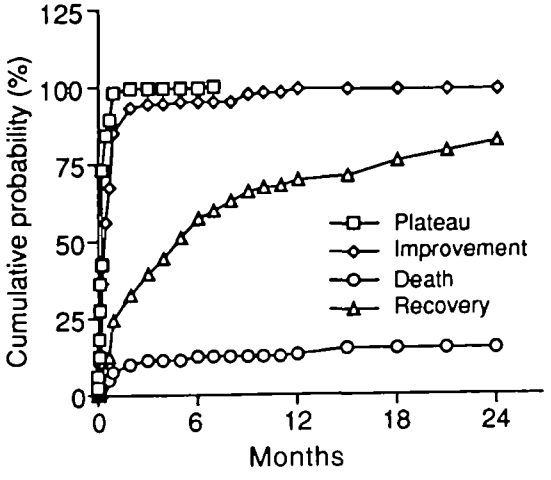

Fig. 1 Cumulative probability of recovery by principal end-points.

only 4% of patients reported remission of symptoms, and 24, 57, 70 and 82% at 4 weeks, 6, 12 and 24 months, respectively.

Age, the presence and type of antecedent disorder, disability and overall disease severity at admission and nadir, and selected electrophysiological findings seemed to affect the chance of recovery significantly (Fig. 2).

The mean time to clinical recovery was 157 days in patients aged <35 years, 208 days in patients aged 35–54 years, and 253 days in patients 55 years and older (F ratio 5.7; $P = 0.01$). Patients in whom gastroenteritis preceded the onset of symptoms had the longest interval to clinical recovery (mean 292 days) compared with a mean of 193 days for upper respiratory infection and 123 days for influenza. Disability at admission did not seem to affect the time to clinical recovery (F ratio 1.0; $P = 0.42$). The same held true for disability at nadir (F ratio 1.4; $P = 0.23$). Multivariate analysis showed that age, antecedent gastroenteritis, disability, an electrophysiological pattern suggesting axonopathy, the latency to nadir and the duration of active disease (i.e. the time to clinical improvement) adversely affected the chance of clinical recovery. The outcome of the disease was better in patients with Guillain–Barré syndrome preceded by influenza (Table 4).

There were 41 patients treated with steroids, 43 with immunoglobulins, 109 with plasma exchange, 73 with treatment combinations and 31 who were left untreated. Patients receiving immunoglobulins seemed to recover sooner than those left untreated or given steroids and/or plasma exchange (Fig. 3). However, inclusion of the main treatments (steroids, plasma exchange and immunoglobulins) in the model did not seem to influence the prognostic significance of the variables affecting the chance of recovery.

Discussion

This is the largest prospective study on the prognosis of Guillain–Barré syndrome in a fairly representative sample of hospitalized patients. Although the original population of our

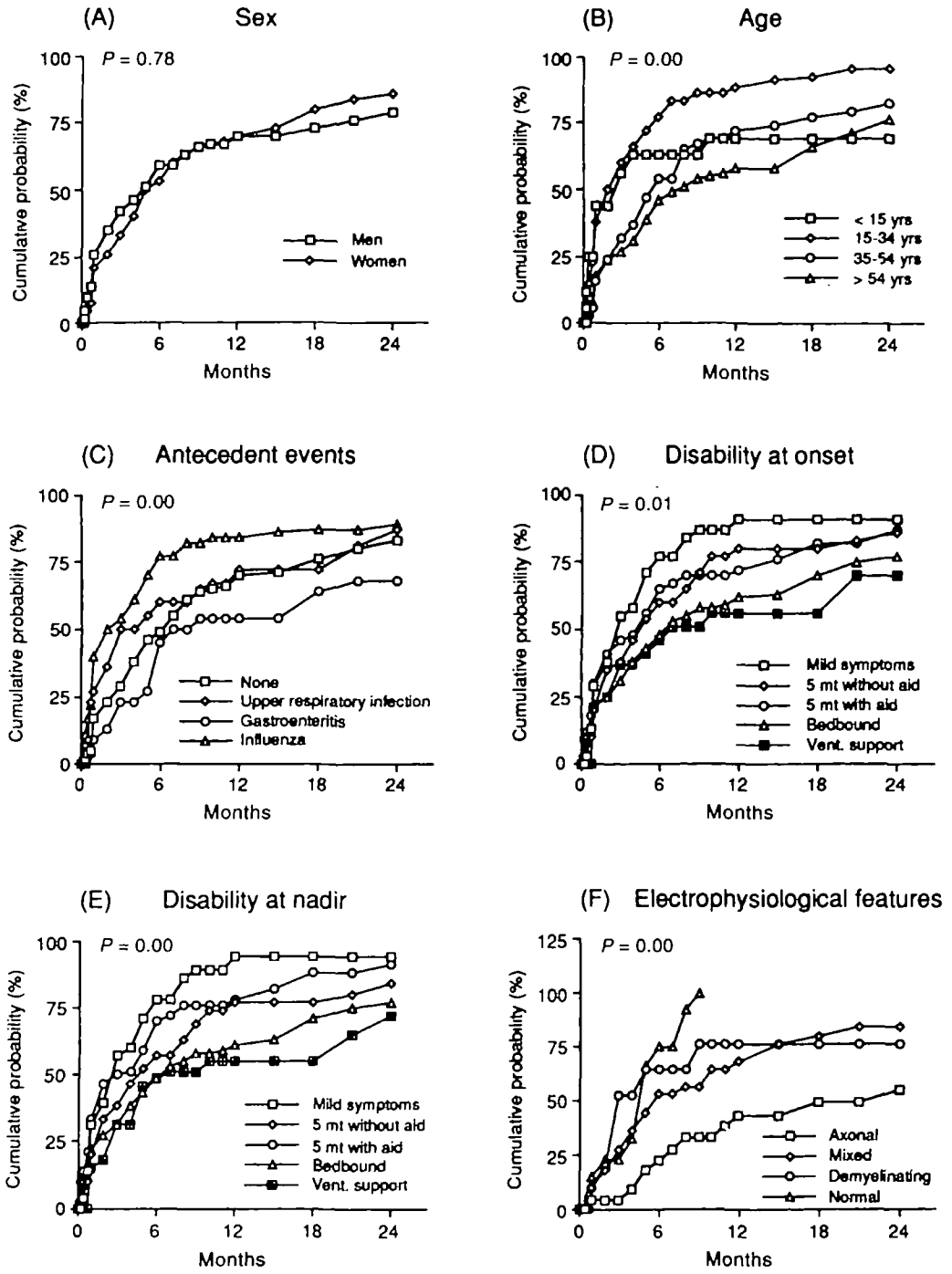

Fig. 2 Cumulative probability of recovery by selected prognostic factors.

cases is unknown, there was a striking similarity between our patients and those from community studies which used similar diagnostic criteria. The age and sex distribution of our Guillain–Barré syndrome patients appears similar to that of the Rochester, Minn., population (Beghi *et al.*, 1985), when the age groups used in the USA study are applied to the present investigation. The outcome of the disease (complete recovery, residua or death) was also remarkably similar in the two populations. An internal comparison between the patients enrolled in the 14 centres around the country and those participating in the incidence study in Emilia Romagna found only minor demographic and clinical differences (larger proportion of men and elderly patients and less severe disease varieties in Emilia Romagna) (Italian Guillain–Barré Study Group, 1995). These findings support the concept that, at least in Italy, every patient with a recognized or suspected diagnosis of Guillain–Barré syndrome tends to be hospitalized. Recent reports from the USA (Koobatian *et al.*,

Table 4 *Prognosis of Guillain–Barré syndrome in Italy: multivariate analysis of the main prognostic predictors*

Variable	Hazard ratio	Confidence interval
Age (years)		
<35	1	
35–54	0.70	0.47–1.06
>54	0.59	0.41–0.86
Antecedent disorders		
Gastroenteritis	0.40	0.23–0.71
Influenza	1.91	0.73–2.69
Other/unknown		
Disability at nadir		
Mild symptoms/signs	1	
5 m without support	0.77	0.45–1.32
5 m with support	0.70	0.43–1.16
Chair/bedbound	0.39	0.24–0.63
Respiratory insuff.	0.24	0.1–0.44
Latency to nadir (weeks)		
<1	1	
1–2	0.71	0.51–0.98
3–4	0.47	0.30–0.73
>4	0.36	0.18–0.69
Duration of active disease (weeks)		
<1	1	
1–2	0.70	0.45–0.90
3–4	0.58	0.36–0.93
>4	0.36	0.15–0.41
Electrodiagnostic features		
Normal	1	
Demyelinating	1.82	0.46–7.17
Axonal	0.14	0.04–0.51
Mixed	0.64	0.22–1.88

Data adjusted for sex and centre; the contribution of antecedent upper respiratory infection and treatments (steroids, plasma exchange, immunoglobulins) to the overall χ^2 value was not significant.

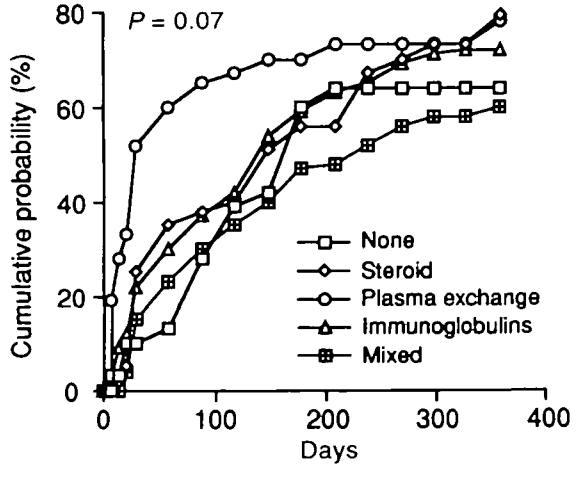

Fig. 3 Cumulative probability of recovery by treatment modalities.

1991) and Sweden (Jiang *et al.*, 1995) indicate that the incidence of Guillain–Barré syndrome calculated from hospital data compares with the highest rates reported in well-defined study populations (Alter, 1990), providing evidence that hospital discharge data are a good basis for epidemiological surveys of Guillain–Barré syndrome.

Based on the present findings, the mean time of progression of the disease, estimated as the time to nadir, was 12 days, 98% of patients achieving a plateau within 4 weeks from the onset of neuritic symptoms. The mean time to nadir was identical to that reported by Ravn (1967) in a retrospective investigation of 127 Danish hospital patients, and by Raphael *et al.* (1986) in 223 patients admitted to a hospital service of neurology and intensive care in France. Similar findings were reported by Kleyweg *et al.* (1989) in 68 Dutch patients, with only minor differences between children (9.6 days) and adults (11 days). The timed proportion of patients progressing to maximal symptoms in this study was also similar to that reported by Eiben and Gersony (1963) in 48 patients admitted to the Cleveland Metropolitan Hospital (79% in 14 days), by Andersson and Sidén (1982) in 60 patients treated for Guillain–Barré syndrome at two university hospitals in Sweden (87% in <20 days), and by Winer *et al.* (1988) in 100 patients notified from hospitals in the south-east England (70% in <14 days and 84% in <21 days).

The similarity of studies conducted in different populations and with different designs seems to confirm the concept that the progression of Guillain–Barré syndrome is independent of the patients' general characteristics and the overall disease severity. However, a shorter time to nadir and a prolonged peak phase seem to predict a more severe prognosis and the likelihood of residua during follow-up (Ravn, 1967; Winer *et al.*, 1985, 1988; Kaur *et al.*, 1986; Raphael *et al.*, 1986). We confirmed these findings. Data are scarce on the time to onset of recovery, as this information cannot be easily traced from retrospective studies. Andersson and Sidén (1982) reported 81% of patients starting recovery within 40 days. Using this interval for reference, 75% of patients started improvement in the present study. The cumulative recovery detected here was 70% by 1 year and 82% by 2 years.

Retrospective studies with shorter observation periods (up to 15 months) which reported recovery in 25–78% of cases (Ravn, 1967; Pleasure *et al.*, 1968; Winer *et al.*, 1985; Kaur *et al.*, 1986; Bradshaw and Jones, 1992) are not easily comparable with this series. The lower recovery rates reported by Raphael *et al.* (1986) (48% by 1 year and 60% by 2 years) may reflect selection bias, as patients admitted to an intensive care department may more frequently represent more severe disease varieties. The better outcome in the Dutch study (Kleyweg *et al.*, 1989) (92% reporting good recovery), on the other hand, may depend on the inclusion of patients with minor symptoms and signs among those who were thought to have recovered. In the only prospective study of Guillain–Barré syndrome (Raphael *et al.*, 1986) which used the same inclusion criteria, the overall outcome was similar (67% of cases recovering completely and 20% remaining significantly disabled by 1 year).

In the present investigation, the chance of recovery was adversely affected by increasing age and disease severity and, where available, by the presence of electrophysiological

features of axonal damage. Also, the type of antecedent illness seemed to influence the outcome of the disease, enhancing (influenza) or hampering (gastroenteritis) clinical recovery. The poorer outcome of Guillain–Barré syndrome in older patients has been reported by others (Ravn, 1967; McKhann *et al.*, 1988; Winer *et al.*, 1988) and may reflect poor axonal outgrowth and regeneration and less effective remyelinization in the elderly (Black and Lasek, 1979; Pestronk *et al.*, 1980). Severity during the active phase has been repeatedly reported to affect the chance of recovery (Ravn, 1967; Pleasure *et al.*, 1968; Andersson and Sidén, 1982; Winer *et al.*, 1985, 1988; Kaur *et al.*, 1986; Raphael *et al.*, 1986; McKhann *et al.*, 1988). This finding falls in line with the recent description of severe Guillain–Barré syndrome varieties, such as the axonal form reported by Feasby *et al.* (1986) and the report by McKhann *et al.* (1993) of a motor and axonal variety of Guillain–Barré syndrome among Chinese children and young adults. The more severe Guillain–Barré syndrome variety following gastroenteritis in our series is also in keeping with other reports (Winer *et al.*, 1988; Palace and Hughes, 1994) that *Campylobacter jejuni* infection, which is the commonest recognized cause of diarrhoea worldwide (Griffin and Ho, 1993), may be associated with acute motor axonal or acute motor and sensory axonal neuropathy (Ho *et al.*, 1995; Rees *et al.*, 1995).

Based on the present findings and the results of other reports, we can thus confirm that Guillain–Barré syndrome is a heterogeneous condition and that older age, antecedent gastroenteritis and electrophysiological evidence of axonopathy may be independently associated with a more severe disease variety and less chance of recovery.

Eleven percent of our patients died, mostly during the acute phase of the disease. The overall mortality in Guillain–Barré syndrome has been reported to range between 1% and 18% in the largest series (Ropper *et al.*, 1991). Dysautonomic syndrome, cardiac arrest and respiratory failure were the leading causes of death.

The high percentage of cases with cardiac arrest associated with dysautonomic syndrome merits comment. These findings cannot be given an univocal interpretation. The diagnosis was based mostly on clinical judgement and was confirmed by autopsy only in a few instances. This may lead to erroneous interpretations of the clinical findings. However, arrhythmias tend to occur in up to 75% of patients with Guillain–Barré syndrome and ECG changes can be detected in as many as 80% of cases (*see* Ropper *et al.*, 1991). These findings may be the manifestations of a dysautonomic pattern caused by the immune process and directed against tissues and organs other than the nervous tissue. Circulating antibodies have been reported against kidney, liver and heart antigens in patients with Guillain–Barré syndrome (van Doorn *et al.*, 1987). All these patients except two were admitted to intensive care units, which runs counter to the suspicion that some deaths might have been prevented by appropriate intensive care management.

Patients who died were mostly older, with more severe symptoms and signs at hospital admission. However, antecedent gastroenteritis and EMG signs of axonal damage did not prevail in lethal Guillain–Barré syndrome compared with the survivors. This apparent difference in the distribution of the prognostic predictors in patients who died compared with those who had residua at last follow-up can be interpreted differently. First, the exact role of axonopathy cannot be predicted here as our findings are based on a limited sample and only few patients who died had a useful EMG record. Secondly, in the absence of serological evidence of *Campylobacter jejuni* infection, it is not possible to confirm whether or not this was the causal agent in the three patients reporting gastroenteritis prior to fatal Guillain–Barré syndrome. Thirdly, the overall severity of Guillain–Barré syndrome and its lethal course are not necessarily correlated. Rapidity of onset, an aspect of Guillain–Barré syndrome that may raise the risk of respiratory failure (Eiben and Gersony, 1963) and mortality, has been reported to affect the overall outcome of the disease by some authors (Winer *et al.*, 1985, 1988; McKhann *et al.*, 1988), but not by others (Pleasure *et al.*, 1968; Kaur *et al.*, 1986).

Several potentially effective treatments, including plasma exchange and immunoglobulins, were used during the course of this study and might have influenced the long-term outcome of the disease. However, there is no evidence of that in our findings, as treatments did not seem to have an independent effect on the chance of remission when they were added in the multivariate analysis model. Indirect evidence of a lack of long-term effects of current treatments can also be found in the similar proportions of patients who recovered in prognostic studies conducted at different times and with different treatments, and do not show any significant trend toward a better long-term outcome in recent years after the introduction of plasma exchange and immunoglobulins.

The long-term effects of treatment can only be assessed through a correct experimental approach and a non-controlled study of this type cannot fully address this issue. However, the results of this and earlier observational studies support the concept that current immune treatments are only effective in shortening the active phase of the disease. Relapses have been repeatedly reported after inadequate cycles of plasma exchange or immunoglobulins. Immune therapies act by removing pathogenic circulating factors (plasma exchange) or possibly promoting anti idiotypic interactions, regulation of B and T cells, blockade of FC receptors and neutralization of pathogenic cytokines (immunoglobulins) (Hartung *et al.*, 1988). These immune mechanisms may not be present in all Guillain–Barré syndrome cases and may not entirely explain the pathogenic mechanism(s) of nerve injury in Guillain–Barré syndrome. A better understanding of the pathogenesis and course of the different Guillain–Barré syndrome varieties could contribute to the development of more rational therapies, which might affect the long-term course of the disease.

In summary, this study provided strong support to the concept that Guillain–Barré syndrome is a syndromic entity

with heterogeneous manifestations, different outcome, and possibly diverse pathogenic mechanisms. Contrary to the old belief that the disease has a favourable outcome in the large majority of patients, several hospital-treated patients may still die or present residua even several months after the onset of symptoms.

Indirect evidence was provided here of the assumption that currently recommended treatments may be effective only during the 'active' phase of the disease. If this is true, efforts are still needed to find compounds with long-term efficacy and with differing mechanisms of action, which could be more appropriately directed against selected disease varieties.

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