

Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria

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Guillain-Barré syndrome is an acute polyradiculoneuropathy with a variable clinical presentation. Accurate diagnostic criteria are essential for patient care and research, including clinical trials and vaccine safety studies. Several diagnostic criteria for Guillain-Barré syndrome have been proposed, including the recent set by the Brighton Collaboration. In the present study we describe in detail the key diagnostic features required to meet these Brighton criteria in a study population of 494 adult patients with Guillain-Barré syndrome, previously included in therapeutic and observational studies. The patients had a median age of 53 years (interquartile range 36–66 years) and males slightly predominated (56%). All patients developed bilateral limb weakness which generally involved both upper and lower extremities. The weakness remained restricted to the legs in 6% and to the arms in 1% of the patients. Decreased reflexes in paretic arms or legs were found initially in 91% of patients and in all patients during follow-up. Ten (2%) patients however showed persistence of normal reflexes in paretic arms. Disease nadir was reached within 2 weeks in 80%, within 4 weeks in 97% and within 6 weeks in all patients. A monophasic disease course occurred in 95% of patients, of whom 10% had a treatment-related fluctuation. A clinical deterioration after 8 weeks of onset of weakness occurred in 23 (5%) patients. Cerebrospinal fluid was examined in 474 (96%) patients. A mild pleocytosis (5 to 50 cells/ μ l) was found in 15%, and none had more than 50 cells/ μ l. An increased cerebrospinal fluid protein concentration was found only in 64% of patients, highly dependent on the timing of the lumbar puncture after onset of weakness (49% at the first day to 88% after 2 weeks). Nerve electrophysiology was compatible with the presence of a neuropathy in 99% of patients, but only 59% fulfilled the current criteria for a distinct subtype of Guillain-Barré syndrome. Patients with a complete data set (335) were classified according to the Brighton criteria, ranging from a high to a low level of diagnostic certainty, as level 1 in 61%, level 2 in 33%, level 3 in none, and level 4 in 6% of patients. Patients categorized in these levels did not differ with respect to proportion of patients with preceding events, initial clinical manifestations or outcome. The observed variability in the key diagnostic features of Guillain-Barré syndrome in the current cohort study, can be used to improve the sensitivity of the diagnostic criteria.

Keywords: Guillain-Barré syndrome; diagnosis; cerebrospinal fluid; electromyography; Brighton collaboration

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Introduction

The diagnosis of Guillain-Barré syndrome remains based on clinical characteristics and ancillary laboratory investigations, nearly one century after the name-giving publication of Georges Charles Guillain and Jean-Alexandre Barré (Guillain *et al.*, 1916). Accurate diagnostic criteria for Guillain-Barré syndrome are important for clinical practice, especially in the early phase of disease when specific treatment is most effective and patients require monitoring to prevent life-threatening complications. In addition, case definitions are required to conduct therapeutic trials and epidemiological studies, especially vaccine safety studies. Early, case-detecting criteria for defining the Guillain-Barré syndrome were developed to investigate the suspected rise in frequency of Guillain-Barré syndrome in persons vaccinated against a swine-origin influenza virus during the national US vaccination campaign in 1976 (Schonberger *et al.*, 1979). The criteria were reaffirmed and expanded in 1990 by Asbury and Cornblath (1990) and are frequently used in research and clinical practice. Recently, the Brighton Collaboration developed a new set of case definitions for Guillain-Barré syndrome, again in response to a possible association between Guillain-Barré syndrome and the H1N1 swine flu vaccination campaign of 2009/2010 (Sejvar *et al.*, 2011). The Brighton Collaboration (www.brightoncollaboration.org) is an international collaboration sponsored by the World Health Organization to facilitate the development, evaluation, and dissemination of high quality internationally standardized case definitions for various illnesses, with the aim of improving vaccine safety. These innovatory 'Brighton criteria' also account for the level of diagnostic certainty based on the presenting findings at clinical and additional examinations, ranging from level 1 (highest level of diagnostic certainty) to level 4 (reported as Guillain-Barré syndrome, possibly due to insufficient data for further classification) (Table 1).

Recent studies indicate that Guillain-Barré syndrome consists of a spectrum of neuropathic disorders that may differ in the underlying pathogenesis and clinical manifestations (Yuki and Hartung, 2012). Designing diagnostic criteria that cover all patients with Guillain-Barré syndrome, therefore, is challenging. Patients with Guillain-Barré syndrome differ from each other regarding the

extent and distribution of weakness, and the presence of autonomic dysfunction, sensory symptoms and cranial nerve deficits. Clinical variants of Guillain-Barré syndrome have been described, including the Fisher Syndrome, bulbar and pharyngeal-brachial variants, which may progress to more characteristic forms of Guillain-Barré syndrome. Nerve biopsy and electrophysiology also identified a variety of subtypes of Guillain-Barré syndrome including acute inflammatory demyelinating polyneuropathy, and an axonal subtype of Guillain-Barré syndrome (Griffin *et al.*, 1995; Hadden *et al.*, 1998). Patients with Guillain-Barré syndrome also differ with respect to the rate of progression, severity at nadir, occurrence of treatment-related fluctuations and the rate and extent of recovery. There are no pathognomonic clinical characteristics for Guillain-Barré syndrome, and at present no biomarkers are available to discriminate Guillain-Barré syndrome from disorders resembling Guillain-Barré syndrome. Depending on the clinical characteristics present in individual patients, there is an extensive list of diseases that may be clinically similar to Guillain-Barré syndrome or its variants and result in misdiagnosis (Levin, 2004).

Patient cohorts have rarely been described in detail with respect to the variation in the key characteristics used to define cases in research and to diagnose patients in clinical practice. In addition, existing diagnostic criteria for Guillain-Barré syndrome have rarely been validated. The objective of the current cohort study is to describe the variation in key diagnostic features in a large cohort of adult patients diagnosed with Guillain-Barré syndrome and classify them according to the diagnostic criteria of the Brighton Collaboration.

Materials and methods

Patients

The study was based on a cohort of 567 patients previously admitted to two randomized clinical trials, one therapeutic pilot study and one observational multicentre study (Table 2) (van der Meché and Schmitz, 1992; The Dutch Guillain-Barré Study Group, 1994; van Koningsveld *et al.*, 2004; Ruts *et al.*, 2010b). Patients had to fulfil the diagnostic criteria from the National Institute of Neurological Disorders and

Table 1 Key diagnostic criteria and Brighton case definitions for Guillain-Barré syndrome

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+ / –
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+ / –
Monophasic course and time between onset-nadir 12 h to 28 days	+	+	+	+ / –
CSF cell count <50/μl	+	+ ^a	–	+ / –
CSF protein concentration > normal value	+	+ / – ^a	–	+ / –
NCS findings consistent with one of the subtypes of GBS	+	+ / –	–	+ / –
Absence of alternative diagnosis for weakness	+	+	+	+

+ present; – absent; + / – present or absent;.

NCS = nerve conduction studies; GBS = Guillain-Barré syndrome.

^a If CSF is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis Guillain-Barré syndrome.

Table 2 Patient cohorts

Reference	Design	n	Aim	Year	Centres	Inclusion criteria ^a	Exclusion criteria ^b	Follow-up	NCS	Excluded cases
van der Meche and Schmitz, 1992	RCT	147	IVIg versus PE	1986–1989	16 Dutch centres	Weakness onset < 2 weeks GBS disability score > 2	Age < 4 year	Week 1–2: 3 × /week Week 3–6: 8, 10, 22, 26	Study entry, Week 1 and 4	10 children One other diagnosis One child
The Dutch Guillain-Barré Study Group, 1994	Open label	25	IVIg and MP (Pilot study)	1990–1992	8 Dutch centres	Weakness onset < 2 weeks GBS disability score > 2	Age < 16 year steroid treatment (or contraindications)	Week: 1–4: 1 × /week Week: 8, 10, 14, 18, 22, 26	Study entry Week 4	16 children Four other diagnosis
van Koningsveld et al., 2004	RCT	225	IVIg and MP versus IVIg	1994–2000	28 Dutch 2 Belgium	Weakness onset < 2 weeks GBS disability score > 2	Age < 6 year steroid treatment (or contraindications)	Week: 1–8: 1 × /week Week: 10, 12, 14, 18, 22, 26	Week 2	Five children 36 other diagnosis
Ruts et al., 2010b	Observational	170	Pain and course	2005–2008	2 German centres ^c 55 Dutch centres	-	Age < 12 year life expectancy < 1 year	Weekly during admission Week: 13, 26, 39 and 52	< 3 weeks	

NCS = nerve conduction studies; RCT = randomized controlled trial; IVIg = intravenous immunoglobulin; PE = plasma exchange; MP = methylprednisolone.

^a Inclusion criteria for all patients were fulfillment of diagnostic criteria for Guillain-Barré syndrome according to the NINDS.

^b Exclusion criteria in the therapeutic studies (1–3) were previous episodes of Guillain-Barré syndrome, allergic reactions to matched blood products, selective IgA deficiency, pregnancy, severe concurrent diseases, or expected difficulties precluding follow-up for the next 6 months.

^c Belgium centres: AZ Sint-Jan Brugge-Oostende AV, Brugge (six inclusions) and Clinique Universitaire St Luc, Brussels, Belgium (10 inclusions); German centres: Medizinische Fakultät Charité, Berlin (13 inclusions) and Ruprecht-Karls Universität, Heidelberg (nine inclusions).

Stroke (NINDS) from 1990 (Asbury and Cornblath, 1990). Patients participating in the therapeutic studies were unable to walk independently and were included within 2 weeks after onset of weakness. In the observational study, patients with mild weakness at admission and clinical variants were also included. For the purpose of this study, we focused on adult patients with Guillain-Barré syndrome and limb weakness. We excluded patients < 18 years of age ($n = 32$), because the clinical presentation of Guillain-Barré syndrome in children may differ from adults (Bradshaw and Jones, 1992; Korinthenberg et al., 2007; Roodbol et al., 2011). In addition, we excluded patients with Fisher Syndrome ($n = 18$), Bickerstaff encephalitis ($n = 2$), acute-onset chronic inflammatory demyelinating polyneuropathy ($n = 10$), myelitis transversa ($n = 3$), uncertain diagnosis ($n = 3$), Sjögren's syndrome ($n = 1$), spinal disc herniation ($n = 1$), vasculitis ($n = 1$), sacral tumour ($n = 1$) and a previous episode of Guillain-Barré syndrome ($n = 1$). Other diagnoses than Guillain-Barré syndrome were excluded by the local neurologists according to routine diagnostic work-up. For the remaining 494 patients all clinical data were collected prospectively and no alternative diagnoses were made during follow-up of at least 6 months. Most patients were included in The Netherlands, but 38 patients were included in two Belgian and two German hospitals. Clinical course was described by using the Guillain-Barré syndrome disability scale (Table 3), a widely accepted scale of disability for patients with Guillain-Barré syndrome ranging from 0 (normal) to 6 (death) (Hughes et al., 1978). Weakness was expressed using the Medical Research Council (MRC) sum score of six bilateral muscles in arms and legs, ranging from 0 (tetraparalytic) to 60 (normal strength) (Kleyweg et al., 1991). Symmetrical weakness was defined as a difference of five or less between the sum of scores of the left-sided versus the right-sided muscle groups. Nadir was defined as the highest Guillain-Barré syndrome disability score or the lowest MRC sum score (excluding small fluctuations of less than five points within the margins of the inter-observer variations) (Hughes et al., 1978; Kleyweg et al., 1991). In case of discrepancies, case record forms were reviewed by a neurologist to determine nadir. Duration of the plateau phase was defined as the number of days between nadir and improvement of five or more points in MRC sum score or one or more points in Guillain-Barré syndrome disability score. Clinical fluctuations were defined previously as an initial improvement or stabilization longer than 1 week followed by secondary deterioration of five points or more in the MRC sum score or one point or more in the Guillain-Barré syndrome disability score (Ruts et al., 2005, 2010a). Treatment-related fluctuations were defined as clinical fluctuations occurring within 8 weeks after start of treatment, and were regarded as part of a monophasic disease course (Ruts et al., 2010a). During the 6 month follow-up 15 patients died and five patients were lost to follow-up (van den Berg et al., 2013). There was no follow-up of reflexes in one of the clinical trials (van Koningsveld et al., 2004). We tried to obtain the missing data of the 479 surviving patients at the clinic where the patients were included. For 335 patients all necessary data were collected to classify these patients according to the Brighton criteria. Patients with missing data that could not be obtained were left out of analysis regarding that particular part of data. Data from nerve conduction studies were used to classify patients in distinct electrophysiological subgroups, including demyelinating polyneuropathy, axonal polyneuropathy and inexcitable nerves (Hadden et al., 1998). Patients showing features of a neuropathy without meeting the criteria for one of these distinct Guillain-Barré syndrome subtypes were categorized as equivocal. An equivocal electrophysiological result was considered to be consistent with Guillain-Barré syndrome. In patients with serial nerve conduction studies, the study around 2 weeks after onset of weakness was chosen for the Brighton classification. CSF

Table 3 Guillain-Barré syndrome disability scale, adapted from Hughes et al. (1978)

0	A healthy state
1	Minor symptoms and capable of running
2	Able to walk 10m or more without assistance but unable to run
3	Able to walk 10m across an open space with help
4	Bedridden or chair bound
5	Requiring assisted ventilation for at least part of the day
6	Dead

count and protein concentration were determined by routine diagnostic methods. The normal value for CSF protein concentration was 0.18–0.58 g/l. Subjects in this study were classified according to Brighton criteria. This was done for the entire cohort and for the subgroup of patients in whom there was a complete data set regarding the six key diagnostic features used in the Brighton criteria. The studies were approved by the local ethical committee, and all patients gave written informed consent.

Statistical analysis

Categorical data were presented as proportions, continuous data as means and standard deviations if normally distributed and as medians and interquartile ranges (IQR) if not-normally distributed. Correlations between MRC sum scores were expressed by the Spearman rank correlation coefficient (r_s). Differences in proportions were tested by the Chi-square or Fisher exact tests and differences in continuous variables by the Mann-Whitney U test. SPSS Statistics 20.0 was used for statistical analyses. A two-sided P -value < 0.05 was considered to be statistically significant.

Results

The demographic and general clinical characteristics of the 494 patients with Guillain-Barré syndrome are provided in Table 4.

Distribution and severity of weakness

The severity of limb weakness at study entry and at nadir was highly variable (Fig. 1). Weakness at nadir ranged from mild severity (MRC sum score ≥ 55) in 25 (5%) patients to tetraparalytic (MRC sum score of 0) in 41 (8%) patients. The median MRC sum score at nadir was 38 with an IQR of 24–48. Four patients were admitted with cranial nerve involvement and initial normal limb strength, but all developed limb weakness within 11 days. Almost all patients presented with symmetrical weakness: 316 (65%) had exactly the same MRC sum score at both sides, and 459 (95%) patients had a difference of two points or less. Four patients presented with asymmetrical limb weakness of more than five points difference, but all became symmetrical within 1 week, except for one patient with persistent unilateral radial nerve palsy in addition to general limb weakness.

At study entry, most patients had a tetraparesis, but 40 (8%) patients presented with a selective paraparesis of the legs. In this subgroup with a paraparetic variant, 34 (85%) patients were

Table 4 Description of patients with Guillain-Barré syndrome ($n = 494$)

Demography		
Male/female ratio		276/218
Age (years) ^a		53 (36–66)
Symptoms of antecedent infection		
Diarrhoea	24%	(118/489)
Upper respiratory tract infection	38%	(183/480)
Neurological symptoms at entry		
GBS disability score		
1	1%	7/490
2	4%	21/490
3	24%	116/490
4	61%	299/490
5	9%	47/490
Cranial nerve involvement	36%	(177/491)
Sensory deficits	67%	(322/480)
Pain	54%	(259/482)
Ventilator dependent	10%	(47/490)
Neurological symptoms at nadir		
Cranial nerve involvement	53%	(258/490)
Ventilator dependent	28%	(138/493)
Treatment		
Plasma exchange	14%	(70)
IVIg	49%	(244)
IVIg and methylprednisolone	33%	(161)
No treatment ^b	4%	(19)
Outcome at 6 months		
Walking without assistance	82%	(403/489)
Death	3%	(15/482)

GBS = Guillain-Barré syndrome.

^a Median (IQR).

^b Patients included in the observational study (Ruts et al., 2010b).

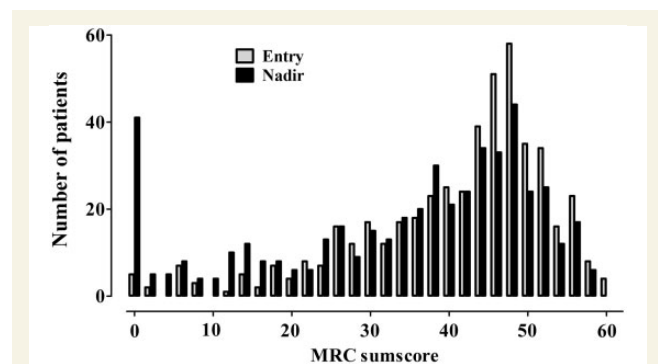


Figure 1 Severity of limb weakness at entry and nadir, expressed as MRC sum score ranging between 0 (tetraplegic) and 60 (normal strength). At entry four patients (1%) had no limb weakness but developed a limb paresis during the disease course. At nadir 41 patients (8%) had a tetraplegia.

unable to walk independently (Guillain-Barré syndrome disability score > 2), despite a relatively high MRC sum score (median 54, IQR 52–56). Nine (23%) of these patients also had normal reflexes in the arms. In 28 (70%) of these patients, the weakness remained restricted to the legs during the entire course of disease.

Weakness restricted to the arms was found in three (1%) patients. Only one of these patients developed leg weakness later; the other two patients were diagnosed as a pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. In patients with a tetraparesis, the MRC sum scores expressing the weakness of severity in arms and legs were correlated ($r_s = 0.66$, $P = 0.01$).

Reflexes

Reflexes and strength were described in detail in 395 (80%) patients for the arms and in 410 (83%) patients for the legs. At study entry, normal reflexes in paretic limbs were observed in 36 (9%) patients. These patients usually had a relatively mild weakness (MRC sum score median 48, IQR 42–52) compared to the patients with decreased reflexes (MRC sum score median 44, IQR 34–49) ($P = 0.03$). Patients with initially normal reflexes also less frequently had sensory deficits (46%) compared to patients with decreased reflexes (69%) ($P = 0.006$). Primary axonal variants (see below) were more frequent in patients with normal reflexes (15%) than in patients with decreased reflexes (6%) ($P = 0.03$). Twenty-six (72%) of these 36 patients with normal reflexes at study entry developed decreased reflexes during the disease course. All patients developed hyporeflexia in the legs, however, 10 had persisting normal reflexes in the arms. Two patients had initial hyperreflexia in weak limbs, in one patient progressing to areflexia 1 day later, the other patient was lost to follow-up regarding the reflexes.

Clinical course

All patients reached their nadir within 6 weeks after onset of weakness. The progressive phase lasted <1 week in half the patients, <2 weeks in 80%, and <4 weeks in 97% (Fig. 2). The duration of the plateau phase was highly variable with a median duration of 7 days (IQR of 6–14 days, full range between 2 days and end of the follow-up period of 6 months). During the

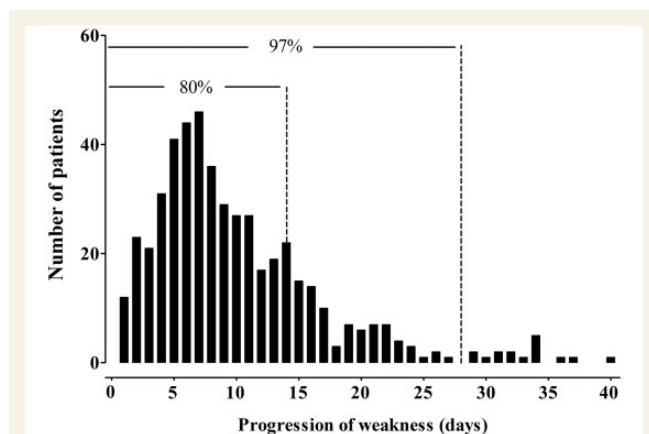


Figure 2 Duration of the progressive phase is defined as the number of days between onset of limb weakness and reaching nadir. The figure shows a skewed distribution in which the duration of the progressive phase is <2 weeks in 80% and <4 weeks in 97% of patients.

recovery phase, secondary deteriorations were seen in 73 (15%) patients. In 50 (68%) of these patients the deterioration was regarded to be a 'treatment-related fluctuation', which by definition occurred within 8 weeks of start of treatment (Ruts *et al.*, 2010a). Patients with a treatment-related fluctuation were considered to have a monophasic disease course that was influenced by a transient effect of treatment. Therefore, in total 472 (95%) patients had a monophasic disease course during the 6 months of follow-up. The remaining 23 (5%) patients had clinical fluctuations more than 8 weeks after start of treatment. In those patients the time interval between onset of weakness and the relapse of muscle weakness was highly variable with a median of 18 weeks (IQR 14–22 weeks, full range 10 weeks to 6 months). Three of these patients had a fluctuation both in the MRC sum score and Guillain-Barré syndrome disability score, whereas the other 20 patients had a fluctuation in only one of these scores.

Cerebrospinal fluid cell count and protein concentration

A lumbar puncture was performed in 474 (96%) patients. The time interval between onset of weakness and lumbar puncture was at a median of 4 days, IQR 2–7 days, and full range 0–32 days. A lumbar puncture within 3 days of onset of weakness was performed in 49% of patients. Overall, 305 (64%) of the 474 patients had an elevated protein concentration in CSF, strongly depending on the timing of the lumbar puncture (Fig. 3). Protein concentrations in CSF higher than normal were found in 49% of patients in the first day, 53% in the first 3 days, and this proportion increased up to 88% at 3 weeks (Fig. 3).

CSF cell counts were available from 455 (92%) patients. In 386 (85%) of these patients, the cell count was within the normal range of <5 cells/ μ l. In 70 (15%) of these patients a mild pleocytosis was found, although all patients had a cell count of <50 cells/ μ l (Table 5). Mild pleocytosis was observed usually in absence of erythrocytes in CSF, although the occurrence of increased

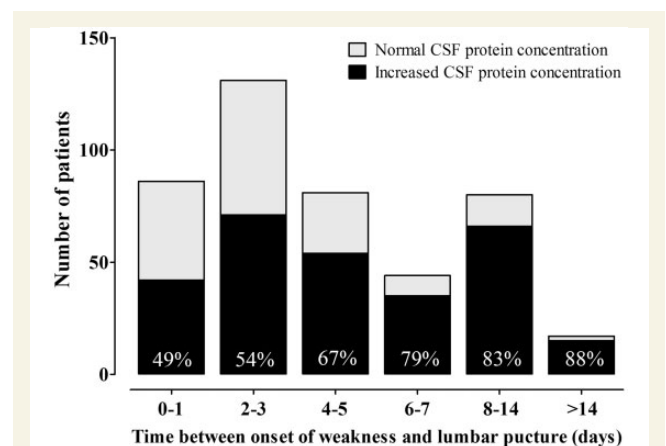


Figure 3 Number of patients and percentages with elevated protein concentration in CSF in relation to the timing of the lumbar puncture after onset of weakness.

Table 5 Diagnostic characteristics in patients with Guillain-Barré syndrome (n = 494)

Neurological symptoms at entry		
Normal strength	1%	(4/490)
Unilateral limb weakness	0%	(1/486)
Asymmetrical severity of limb muscle weakness	1%	(5/486)
Weakness in arms and legs	90%	(443/490)
Weakness in legs only	8%	(40/490)
Weakness in arms only	1%	(3/490)
Severity of weakness (MRC sum score) ^a	44 (35–49)	(490)
Normal tendon reflexes in weak arms	9%	(35/395)
Normal tendon reflexes in weak legs	2%	(7/410)
Duration of progressive phase		
Number of days between onset of weakness and entry ^a	5 (3–8)	(493)
Number of days between entry and nadir ^{a,b}	0 (0–6)	(492)
Number of days between onset of weakness and nadir ^{a,b}	8 (5–13)	(491)
Neurological symptoms at nadir^b		
Limb weakness	100%	(494)
Weakness in legs only	6%	(28/494)
Weakness in arms only	1%	(2/494)
Severity of weakness (MRC sum score) ^a	39 (24–48)	(491)
Normal tendon reflexes in weak arms	2%	(10/388)
Normal tendon reflexes in weak legs	0%	(0/406)
Duration of nadir (days) ^c	7 (6–14)	(472)
Fluctuations in clinical course		
Monophasic course	85%	(421/494)
Treatment related fluctuations within 8 weeks after treatment	10%	(50/494)
Fluctuations later than 8 weeks after treatment	5%	(23/494)
Cerebrospinal fluid examination^d		
Cell count <5/μl	85%	(385/455)
Cell count between 5–10/μl	8%	(36/455)
Cell count between 10–30/μl	6%	(28/455)
Cell count between 30–50/μl	1%	(6/455)
Cell count >50/μl	0%	(0/455)
Protein concentration > normal value	64%	(305/474)
Nerve conduction studies^e		
Normal	1%	(4/440)
Demyelinating	48%	(213/440)
Axonal	6%	(27/440)
Inexcitable	4%	(16/440)
Equivocal	41%	(180/440)

IVIg = intravenous immunoglobulin.

^a Median (interquartial range).

^b Nadir was defined as the highest Guillain-Barré syndrome disability score or the lowest MRC sum score.

^c Duration of nadir was defined as the number of days between reaching nadir and improving at least 1 point in Guillain-Barré syndrome disability score or 5 points in MRC sum score.

^d CSF was examined for cell count in 455 (92%) of patients and for protein concentrations in 474 (96%) of patients.

^e Nerve conduction studies were conducted in 440 (89%) of patients and classified as demyelinating, axonal or inexcitable, equivocal or normal (Hadden *et al.*, 1998).

erythrocyte cell counts caused by a traumatic puncture was not recorded systematically. There was no relation between the cell count and the timing of the lumbar puncture.

The classic 'cytoalbuminologic dissociation', defined as the combination of an increased protein concentration and a cell count <50 cells/μl, was observed only in 290 (64%) of these 455 patients. The proportion of patients with cytoalbuminologic dissociation was fully dependent on the protein concentration and thereby timing of the lumbar puncture (Fig. 3), as no patient had a pleocytosis >50 cells/μl.

Nerve conduction studies

Results of routine nerve conduction studies were available from 440 (89%) patients. The median time between onset of weakness and these examinations was 13 days (IQR 8–18 days). Only four (1%) patients had a normal nerve electrophysiology (conducted at 2, 18, 19 and 30 days after onset of weakness). Patients with a normal EMG had significantly milder weakness at nadir (median MRC sum score of 51, range 43–53) compared to patients with an abnormal nerve conduction study ($P = 0.04$). Acute inflammatory

demyelinating polyneuropathy was the predominant subtype, but only 213 (48%) patients fulfilled the specific diagnostic criteria for a demyelinating polyneuropathy. An axonal polyneuropathy was found in 27 (6%) patients and 16 (4%) patients had inexcitable nerves (Hadden *et al.*, 1998). A subgroup of 180 (41%) patients showed an abnormal nerve electrophysiology compatible with peripheral nerve (root) involvement, but did not fulfil the criteria for one of the distinct subtypes (demyelinating, axonal, or inexcitable). The proportion of patients with these equivocal electrophysiology findings decreased after 3 weeks of weakness onset (Fig. 4).

In the first two studies (between 1986 and 1992), serial nerve conduction studies were performed as part of the study protocol (Table 2). This resulted in 128 of the 160 (80%) patients with serial nerve conduction studies. Serial nerve conduction resulted in a change of subtype classification in 77 (60%) patients. Sixty-four of these patients (83%) switched between an equivocal and demyelinating, axonal or an inexcitable classification or vice versa. Five patients (6%) changed from a demyelinating to an axonal classification and three (4%) patients changed from an axonal to a demyelinating classification. Five (6%) patients changed from an inexcitable to a demyelinating or an axonal classification.

Classification of cases according to the Brighton criteria

The classification according to the Brighton criteria is influenced by completeness of the data. To determine the optimal performance of the Brighton criteria, we excluded 159 (32%) of the 494 patients in which necessary information required to meet one or more of the Brighton criteria was missing: reflexes ($n = 67$), reflexes and CSF ($n = 4$), reflexes and nerve electrophysiology ($n = 12$), clinical course ($n = 1$), clinical course and nerve electrophysiology ($n = 1$), nerve electrophysiology ($n = 38$), CSF ($n = 33$), nerve electrophysiology and CSF ($n = 3$), nerve electrophysiology

and CSF and reflexes ($n = 1$). The remaining 335 patients were classified in four levels of diagnostic certainty according to the Brighton criteria. Criteria for level 1 were met by 205 (61%) patients, for level 2 by 111 (33%) as a result of the normal protein concentration, for level 3 by none and for level 4 by 19 (6%) patients because of a prolonged progressive phase ($n = 6$) or late fluctuations that deviate from a monophasic disease course ($n = 13$) (Table 6). The patient groups in these various diagnostic levels did not differ regarding: age, sex, severity of disease, proportion of ventilator dependency or outcome at 6 months (defined by Guillain-Barré syndrome disability score). Preceding upper respiratory tract infections were seen in 68/203 (34%) of patients in level 1, in 47/107 (44%) patients in level 2 and 6/19 in level 4 (32%). Antecedent diarrhoea was seen in 41/204 (20%) patients in level 1, in 34/111 (31%) patients in level 2 and in 3/19 patients in level 4. Proportions of both preceding symptoms of infections were not significantly different between the Brighton levels. To illustrate the effect of missing data on the level classification, we also showed the results for the whole group of 494, including the 159 patients with missing data (Table 6). This subgroup of patients with missing values did not differ from the subgroup with complete data sets regarding preceding events, demographic characteristics, clinical course and outcome.

Discussion

The current study examined the clinical, electrophysiological and laboratory features in one of the largest cohorts of adult patients with Guillain-Barré syndrome. This study affirmed that the diagnostic criteria for Guillain-Barré syndrome developed by the NINDS in 1990 were met by the majority of patients with certain caveats (Asbury and Cornblath, 1990). In our cohort, 97% of patients reached the nadir of their disease within 4 weeks. At admission, 99% had a symmetrical limb weakness and 91% had reduced

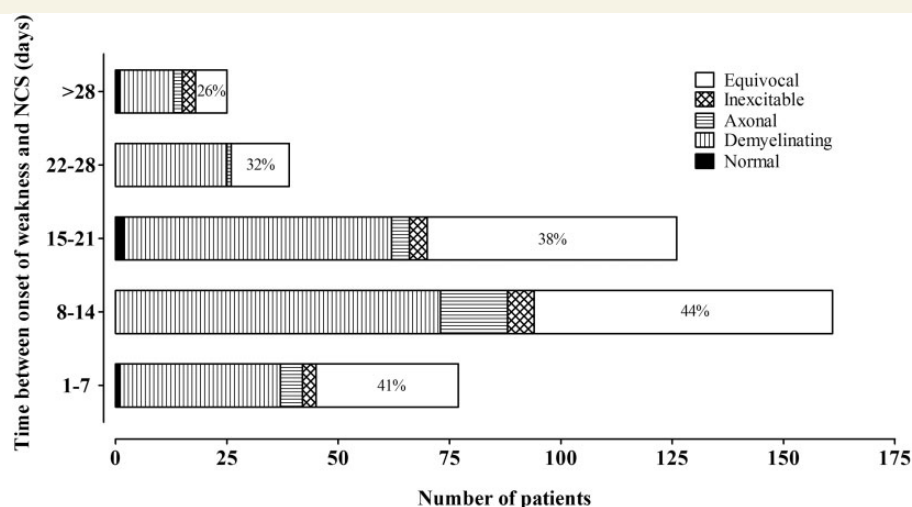


Figure 4 Classification of nerve electrophysiology subtypes in relation to timing of nerve conduction study after onset of weakness. The proportions of patients with an equivocal result are given in percentages, indicating abnormal nerve conduction but not fulfilling the criteria for one of the specific subtypes of Guillain-Barré syndrome. NCS = nerve conduction studies.

Table 6 Classification of patients with Guillain-Barré syndrome according to the Brighton criteria

Brighton level	Data complete (n = 335)	All patients (n = 494)
Level 1	61% (205)	41% (205)
AIDP, axonal, inexcitable	36% (120)	24% (120)
Equivocal NCS	25% (85)	17% (85)
Level 2	33% (111)	36% (177)
Normal NCS	0% (1)	0% (1)
Normal CSF protein concentration	33% (110)	25% (123)
NCS missing	–	5% (24)
CSF missing and NCS consistent with GBS	–	6% (29)
Levels 3	0% (0)	1% (3)
NCS and CSF missing	–	0% (2)
Normal NCS and missing CSF	–	0% (1)
Level 4	6% (19)	22% (109)
Progressive phase > 28 days	2% (6)	3% (13)
No monophasic disease course	4% (13)	5% (23)
Reflexes missing	–	15% (71)
Clinical course missing	–	0% (2)

Patients with Guillain-Barré syndrome were classified in four levels according to the cases definitions of the Brighton Collaboration (Sevjar *et al.*, 2011). This classification is influenced by the completeness of the data, and for the results are therefore given for the patients in whom all data were available ($n = 335$) and for all patients together ($n = 494$). Reasons for not reaching a higher level were specified for each level. Patients reaching level 1 were subdivided in two groups: those who met the criteria for one of the predefined electrophysiological subtypes of Guillain-Barré syndrome, and those with an equivocal electrophysiology (Sevjar *et al.*, 2011).

AIDP = acute inflammatory demyelinating polyneuropathy; NCS = nerve conduction studies; GBS = Guillain-Barré syndrome.

reflexes in all paretic limbs. During disease progression, all patients developed reduced reflexes in the legs, although a few patients retained upper limb reflexes throughout their illness despite arm weakness. All patients showed recovery to some extent and 95% had a monophasic disease course, some with a transient treatment-related fluctuation in the acute stage. All patients with an examination of the CSF showed a cell count <50 cells/ μl and almost all nerve conduction studies showed evidence for a neuropathy. Patients were diagnosed by a neurologist according to routine diagnostic work-up. Because of the follow-up period of at least 6 months, it is highly unlikely that patients had another disorder than Guillain-Barré syndrome. Our study cohort may have been subject to selection bias. Patients included in the therapeutic clinical trials may have had different symptomatology compared to patients who do not participate in such trials. Most patients (94%) in our cohort were unable to walk independently, and we may have excluded milder cases with different symptomatology. Also patients with a CSF cell count over 50 cells/ μl might not be included in these clinical trials, although this was not one of the specific exclusion criteria. The clinical and electrophysiological phenotype of Guillain-Barré syndrome is influenced by the geographical origin of the patients, and in the current study all patients were inhabitants of The Netherlands, Belgium or Germany. The clinical manifestations may also differ in children, which have been excluded in the current study. Patients who had an atypical

presentation not meeting the NINDS criteria may not have entered the trials. The primary aim of the NINDS was to develop diagnostic criteria for research purposes with a high specificity, not to capture all cases in clinical practice. On the other hand, the NINDS criteria are not very strict in the sense that predefined clinical features are categorized as 'supporting the diagnosis' or 'casting doubt on the diagnosis' without specifying the decision rules for inclusion or exclusion of individual patients. This explains why a cohort with such a variety of clinical symptoms was included.

Since 1990 many studies showed the high variability of Guillain-Barré syndrome, including variants, 'formes frustes' and overlap syndromes, with an equally large variation in type of preceding infections and specificity of antibodies to nerve glycolipids (Hughes and Cornblath, 2005; Willison, 2005; van Doorn *et al.*, 2008). In 2009 the Brighton Collaboration took the initiative to develop a new set of criteria to better identify patients for vaccine safety studies. Important advantages of the Brighton criteria are the explicit case definitions and the classification in four levels of diagnostic certainty depending on the patient characteristics and the availability of the data. As the classification is partly determined by missing data, we validated the criteria separately in the subgroup of 335 patients with a complete data set for all key diagnostic features, which is a strength of our study. Despite the completeness of the data and the certainty of the diagnosis in this subgroup of patients, only 61% could be classified as level 1. The predominant cause for not reaching this level of highest diagnostic certainty was a normal protein concentration in CSF (33%). Other, less frequent causes were a prolonged progressive phase of >28 days (2%), and the absence of a monophasic disease course (clinical deterioration beyond 8 weeks of onset of weakness) (4%). Those using the Brighton classification for nerve electrophysiology may find it confusing as described in its current context. As written, we initially reserved Brighton level 1 only for patients who fulfilled the electrophysiological criteria for one of the distinct Guillain-Barré syndrome subtypes. However, personal communication with Cornblath and Sevjar clarified their intention to classify all patients with electrophysiological results consistent with a neuropathy for level 1, also including the 'equivocal' class of Hadden *et al.* (1998). In our study, this resulted in 25% of patients in level 1. Patients from various levels did not differ regarding clinical severity or outcome, indicating that they are equally important for future vaccine safety studies. Applying the criteria to all 494 patients resulted in 41% level 1, 36% level 2, 1% level 3, and 22% level 4, illustrating the importance of missing data in the performance of these criteria. In a previous Dutch study on the Guillain-Barré syndrome background incidence rate, not overlapping with the current studied cohort, only six (26%) of 23 patients reached level 1 or 2, largely because of missing data (van der Maas *et al.*, 2011). Also in studies from Korea and India, a considerable proportion of patients were classified as level 4 (14% and 24%, respectively), partly because additional investigations were frequently not performed or results not available (Choe *et al.*, 2011; Mateen *et al.*, 2011). However, level 3 of the Brighton criteria is dependent only on clinical criteria and does not rely on additional investigations. This category was designed particularly with resource-poor settings in mind, in situations where

electrophysiological and CSF examination may be difficult, impractical, or unavailable. This study emphasizes the fact that accurate and thorough documentation of clinical signs should allow for better classification of Guillain-Barré syndrome in both developed, and in developing countries. In The Netherlands additional investigations such as CSF examination or serial nerve physiology may not be conducted routinely in clinical practice if alternative diagnoses are not suspected.

The current study identified subgroups of patients with characteristics that may be considered atypical for Guillain-Barré syndrome, and may cause initial diagnostic confusion. One subgroup of 8% presented with a paraparesis of the legs, which in more than half of the patients remained restricted to the legs during a follow-up of at least 6 months. The majority of these patients were unable to walk independently, but had normal strength in the arms. All these patients developed decreased reflexes of the legs and fulfilled the other diagnostic criteria for Guillain-Barré syndrome and showed recovery after treatment. Other diagnoses than Guillain-Barré syndrome were excluded in all cases. A similar paraparetic variant was previously described by Ropper (1994), although the frequency and pathogenesis so far remained elusive. In contrast, some patients had weakness restricted to the arms and were in part identified as having a pharyngeal-cervical-brachial variant. Another subgroup of 9% of patients presented with paretic limbs without reduced limb reflexes. These patients frequently had a relatively mild, pure motor and axonal variant of Guillain-Barré syndrome. Most patients with initial normal reflexes developed areflexia during follow-up, but 10 patients had persistent normal reflexes in paretic arms. Retrospectively, 10 included patients did not fulfil the criteria of NINDS because of persistent normal reflexes in weak arms (Asbury and Cornblath, 1990). These patients were all tetraplegic, had decreased reflexes in weak legs, without any alternative diagnosis made during follow-up and were therefore not excluded from this study. Also the Brighton collaboration has not specified explicitly if such patients fulfil the criteria for reduced reflexes or not. From our perspective they do because of the reduced reflexes in the weak legs and therefore could reach a level 1 to 3 (depending on the CSF and nerve conduction study results).

Recently, some patients from Japan and Italy have been described with Guillain-Barré syndrome in combination with limb hyperreflexia (without Babinski sign or spasticity) (Yuki *et al.*, 2012). In the current study, two patients with initial hyperreflexia in weak limbs were reported, in one patient rapidly progressing to areflexia, the other patient was lost to follow-up regarding the reflexes. Some patients may have additional involvement of the CNS, such as in overlap syndromes with Bickerstaff encephalitis or spinal cord involvement (Odaka *et al.*, 2003), but pre-existent brisk reflexes caused by concomitant unrelated disorders, including cervical myelopathy, should be excluded.

Guillain-Barré syndrome is considered to be an acute monophasic disorder, induced by a transient immune response against an acute environmental trigger. Our study shows that the expected clinical course with a successive progressive, plateau and recovery phase is remarkably variable. Eighty per cent of patients already reached nadir within 2 weeks, but at the other end of the spectrum 4% had a progressive phase of 4 to 6 weeks, which may

represent a 'subacute' variant of Guillain-Barré syndrome (Hughes *et al.*, 1992). The duration of the plateau phase was equally variable: most patients start recovering within less than a week after reaching nadir, but 6 months follow-up without clear signs of recovery is still compatible with the diagnosis of Guillain-Barré syndrome. All patients recovered at some stage, yet secondary deteriorations during the follow-up period were seen in 15% of patients. Two-thirds of these patients (10%) had a typical treatment related fluctuation, in which the secondary progression may be attributed to a transient effect of treatment that lasted shorter than the active disease phase (Kleyweg and van der Meché, 1991). One-third of deteriorations (5%), however, occurred >8 weeks after treatment. Such prolonged deteriorations may have previously been reported as the first episodes of acute onset chronic immune demyelinating polyneuropathy (Ruts *et al.*, 2010a). In the current study, however, the patients with acute onset chronic immune demyelinating polyneuropathy were excluded. These deteriorations may have been caused by a more persistent or relapsing-remitting active state of disease, possibly influenced by secondary infections or other complications. The observed fluctuations may in part also be explained by the clinimetric limitations of the MRC sum score and Guillain-Barré syndrome disability score (Kleyweg *et al.*, 1991; Vanhoutte *et al.*, 2012). Local clinical care facilities and treatment options may also influence the clinical course and outcome of Guillain-Barré syndrome.

CSF examination may be useful in cases of clinical uncertainty about the diagnosis, especially to exclude other causes associated with CSF pleocytosis, such as infectious polyradiculitis and acute poliomyelitis (Guillain *et al.*, 1916). In all 455 patients where CSF was examined, the cell count was <50 cells/ μ l, confirming the specificity of this finding. CSF cell counts between 5 and 50 cells/ μ l, however, were found in 15% of patients, indicating that a mild pleocytosis is compatible with the diagnosis of Guillain-Barré syndrome. The 'cyto-albuminologic dissociation' in CSF, commonly regarded as one of the hallmarks of Guillain-Barré syndrome, was found in less than half of the patients when tested within the first day after onset of weakness. Only after a week of weakness this typical finding for Guillain-Barré syndrome reaches a sensitivity of 80%. Repeating a lumbar puncture in case of a normal CSF to confirm the diagnosis may be confusing as both the cell count and the protein concentration may be influenced by the first puncture and by treatment with IVIg (intravenous immunoglobulin) (Ben Menachem *et al.*, 1989; Sekul *et al.*, 1994; Wurster and Haas 1994). Future improvement may come from specific biomarkers for axonal degeneration or demyelination (Brettschneider *et al.*, 2009).

Routine nerve electrophysiology was performed in 440 patients, usually in the second or third week after onset of weakness. In almost all patients the findings were compatible with the presence of a neuropathy. The predominant subtype was acute inflammatory demyelinating polyneuropathy (48%), confirming previous studies in patients from Western countries (Hadden *et al.*, 1998). Forty-one per cent of the patients, however, did not meet the criteria for one of the defined subtypes of Guillain-Barré syndrome. In current clinical practice the value of subtyping by nerve electrophysiology is uncertain. Nerve physiology might

have prognostic relevance (Cornblath *et al.*, 1988). Importantly, at present there are no definite agreed-upon diagnostic electrophysiological criteria for the diagnosis of Guillain-Barré syndrome. All current electrophysiological criteria focus on the discrimination between axonal and demyelinating subtypes of Guillain-Barré syndrome. The subtyping of Guillain-Barré syndrome is complex as (i) the electrophysiology examination requires high standards and skills; (ii) various classification systems have been developed; and (iii) patients with axonal variants may initially show features usually attributed to demyelination, such as conduction blocks and prolonged distal motor latency (Kokubun *et al.*, 2010). In our cohort of 128 patients with serial nerve conduction studies, five patients showed an initial demyelinating polyneuropathy but had a classification change toward an axonal polyneuropathy at follow-up. These patients possibly have reversible conduction failure that is not taken into account by the current criteria (Hadden *et al.*, 1998). Far more patients, however, changed from equivocal to a specific Guillain-Barré syndrome subtype classification when serial nerve conduction studies were conducted. The diagnostic value of electrophysiology may be improved by serial measurements and more sensitive techniques and by developing criteria both for Guillain-Barré syndrome in general and optimizing the criteria for the various subtypes of Guillain-Barré syndrome (Uncini and Kuwabara, 2012).

Early and accurate recognition of Guillain-Barré syndrome may be challenging in such a clinically heterogeneous disorder, especially when there are also alternative diagnoses possible. The current study shows that, although in a minority, Guillain-Barré syndrome may present with an extended progressive phase up to 6 weeks, weakness of the legs only and initial normal reflexes, and may show some clinical fluctuations later in the disease course. The clinical decision to admit, monitor and treat the patient will be made before the duration of the progressive phase and the presence of a monophasic disease course is known. Without accurate biomarkers, the clinical features will remain the hallmark for the diagnosis of Guillain-Barré syndrome. As such, it will be important to emphasize careful documentation of clinical features of suspected cases of Guillain-Barré syndrome to physicians, to be able to have all necessary clinical data available for classification. Additional investigations may play a crucial role in the diagnosis of Guillain-Barré syndrome. It would be helpful if electrophysiological criteria were developed that could support the diagnosis of Guillain-Barré syndrome in general, instead of discriminating between the variant subtypes of Guillain-Barré syndrome (Franssen, 2012). The current study underscores that the CSF is examined mainly to exclude disorders that are associated with pleocytosis, instead of seeking confirmation of the diagnosis Guillain-Barré syndrome by demonstrating an increased protein concentration. Guidelines for the diagnostic work-up, documentation and management of Guillain-Barré syndrome in clinical practice are therefore most needed.

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