doi:10.1093/brain/awy232 BRAIN 2018: 141; 2866–2877 | 2866

BRAIN
A JOURNAL OF NEUROLOGY

Regional variation of Guillain-Barré syndrome

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[#]Appendix 1.

Guillain-Barré syndrome is a heterogeneous disorder regarding the clinical presentation, electrophysiological subtype and outcome. Previous single country reports indicate that Guillain-Barré syndrome may differ among regions, but no systematic comparative studies have been conducted. Comparative studies are required to identify factors determining disease susceptibility, variation and prognosis, and to improve diagnostic criteria. The International Guillain-Barré Syndrome Outcome Study is a prospective, observational cohort study including all patients within the diagnostic spectrum, aiming to describe the heterogeneity of Guillain-Barré syndrome worldwide. The current study was based on the first 1000 inclusions with a follow-up of at least 1 year and confirmed the variation in clinical presentation, course and outcome between patients. The full clinical spectrum of Guillain-Barré syndrome was observed in patients from all countries participating in the International Guillain-Barré Syndrome Outcome Study, but the frequency of variants differed between regions. We compared three regions based on geography, income and previous reports of Guillain-Barré syndrome subtypes: 'Europe/Americas', 'Asia' (without Bangladesh), and 'Bangladesh'. We excluded 75 (8%) patients because of alternative diagnoses, protocol violations, or missing data. The predominant clinical variant was sensorimotor in Europe/Americas ($n = 387/562$, 69%) and Asia ($n = 27/63$, 43%), and pure motor in Bangladesh ($n = 74/107$, 69%). Miller Fisher syndrome and Miller Fisher-Guillain-Barré overlap syndrome were more common in Asia ($n = 14/63$, 22%) than in the other two regions (Europe/Americas: $n = 64/562$, 11%; Bangladesh: $n = 1/107$, 1%) ($P < 0.001$). The predominant electrophysiological subtype was demyelinating in all regions (Europe/Americas: $n = 312/573$, 55%; Asia: $n = 29/65$, 45%; Bangladesh: $n = 38/94$, 40%). The axonal subtype occurred more often in Bangladesh ($n = 34/94$, 36%) than in Europe/Americas ($n = 33/573$, 6%) and other Asian countries ($n = 4/65$, 6%) ($P < 0.001$). In all regions, patients with the axonal subtype were younger, had fewer sensory deficits, and showed a trend towards poorer recovery compared to patients with the demyelinating subtype. The proportion of patients able to walk unaided after 1 year varied between Asia ($n = 31/34$, 91%), Europe/Americas ($n = 334/404$, 83%) and Bangladesh ($n = 67/97$, 69%) ($P = 0.003$). A similar variation was seen for mortality, being higher in Bangladesh ($n = 19/114$, 17%) than in Europe/Americas ($n = 23/486$, 5%) and Asia ($n = 1/45$, 2%) ($P < 0.001$). This study showed that factors related to geography have a major influence on clinical phenotype, disease severity, electrophysiological subtype, and outcome of Guillain-Barré syndrome.

Received May 11, 2018. Revised June 21, 2018. Accepted July 23, 2018

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Keywords: polyradiculoneuropathy; demyelination; axonal degeneration; clinical course; outcome

Abbreviations: GBS = Guillain-Barré syndrome; IGOS = International Guillain-Barré Syndrome Outcome Study; IVIg = intravenous immunoglobulin; MFS = Miller Fisher syndrome; MRC = medical research council; NCS = nerve conduction studies

Introduction

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy that yearly affects ~100 000 people worldwide (Sejvar *et al.*, 2011*a*). While GBS is an established clinical syndrome with defined diagnostic criteria (Asbury and Cornblath, 1990; Sejvar *et al.*, 2011*b*), patients differ considerably in clinical presentation, disease course, and outcome. Patients may have clinical variants of GBS, including Miller Fisher syndrome (MFS) and pure motor, paraparetic, or pharyngeal-cervical-brachial forms (Willison *et al.*, 2016). The electrophysiological characteristics of GBS are likewise heterogeneous and include two major subtypes with demyelinating or axonal features (Willison *et al.*, 2016). Some patients are mildly affected and recover spontaneously, but others develop tetraplegia and respiratory or autonomic failure requiring intensive care and remain severely disabled or die despite treatment (van den Berg *et al.*, 2014). The time to improvement is reduced with plasma exchange or intravenous immunoglobulin (IVIg) (Hughes *et al.*, 2007, 2014; Chevret *et al.*, 2017) but most patients in low-income countries receive supportive care only (Islam *et al.*, 2016).

Comparison of previous studies conducted in single countries suggests that the variation of GBS may be influenced by factors related to the geographical origin of patients, such as endemic infections or unusual epidemics like the recent GBS peaks related to Zika virus (Cao-Lormeau *et al.*, 2016; Parra *et al.*, 2016). These studies illustrate a wide variability in prevalence of clinical variants and electrophysiological subtypes of GBS between regions, suggesting that sensorimotor and demyelinating GBS predominate in Europe and North America, whereas pure motor and axonal GBS are more frequent in Asian and South American countries (Lyu *et al.*, 1997; Hadden *et al.*, 1998; Bogliun *et al.*, 2004; Hughes and Cornblath, 2005; Islam *et al.*, 2010; Sekiguchi *et al.*, 2012; Kuwabara and Yuki, 2013; Mitsui *et al.*, 2015; Willison *et al.*, 2016; Liu *et al.*, 2018). However, these single country studies had different study designs, inclusion criteria and definitions of GBS variants (Ho *et al.*, 1995; Hadden *et al.*, 1998). Therefore, although valuable, these studies have intrinsic limitations and do not describe the full spectrum and geographical variation of GBS. Demonstrating the geographical variation is required to clarify the role of environmental and host factors in severity and subtypes of GBS, and point to the need for different diagnostic criteria and treatments in various parts of the world.

The International GBS Outcome Study (IGOS) is a multicentre, prospective, observational cohort study investigating factors that determine and predict the clinical course, subtype, and outcome of GBS (Jacobs *et al.*, 2017). The aim of the current study was to use the collected data from the first 1000 patient inclusions in IGOS with a follow-up of 1 year to describe the heterogeneity of GBS and to compare the clinical presentation, electrophysiological subtypes, disease course, and outcome between patients from different geographical regions.

Materials and methods

This study is registered at ClinicalTrials.gov with identifier: NCT01582763

Study design

The IGOS study protocol has been described elsewhere (Jacobs *et al.*, 2017). The current study was based on the analysis of the first 1000 included patients. Patients fulfilled diagnostic criteria for GBS or its variants and were included within 2 weeks from onset (Asbury and Cornblath, 1990; Sejvar *et al.*, 2011*b*; Wakerley *et al.*, 2014). Patients were enrolled between May 2012 and July 2015 from 135 active study sites in 18 countries across five continents. The study was approved by the review boards of Erasmus University Medical Centre, Rotterdam, The Netherlands, and the local institutional review boards of participating hospitals or universities. Written informed consent was obtained from all patients.

Data collection

Data were collected regarding demography, antecedent events, and neurological symptoms and signs of GBS at study entry and at 1, 2, 4, 8, 13, 26 and 52 weeks (Jacobs *et al.*, 2017). Muscle strength was recorded by the Medical Research Council (MRC) score (Kleyweg *et al.*, 1991) and disability by the GBS disability score (Hughes *et al.*, 1978). Presence of autonomic dysfunction, defined as cardiac, blood pressure, gastro-enteric, bladder, pupil, or other (e.g. excessive perspiration) abnormalities, was left to the decision of the treating physician. Results of routine CSF examination and nerve conduction studies (NCS) were collected. We defined an elevated CSF protein level as >0.45 g/l (Hadden *et al.*, 2001; Jacobs *et al.*, 2017). A cytoalbuminological dissociation was defined as a CSF cell count <50 cells/μl combined with a CSF protein level >0.45 g/l. To determine the electrophysiological subtype, we used raw data of the first NCS, local reference values, and an algorithm to classify each NCS into demyelinating, axonal, inexcitable, equivocal, or normal subtype, according to criteria of Hadden *et al.* (1998). Patients with axonal and demyelinating neuropathy were compared for each region, to specify previously reported differences between these subtypes.

Disease nadir was defined by the lowest MRC sum score during the first 4 weeks from study entry. When two visits had equal lowest MRC sum scores, the first visit score was used. Patients who had reached nadir before study entry and patients lost to follow-up in the first 4 weeks were excluded from the analysis of nadir.

Asymmetrical weakness was defined as a difference in MRC sum scores of $\geqslant 5$ points between the right- versus left-sided muscles (Fokke *et al.*, 2014).

Clinical variants were adopted from the reported variants at visit Week 2, substantiated by recorded data, and were defined as: (1) sensorimotor; (2) pure motor; (3) MFS or MFS-GBS overlap syndrome; and (4) other, which included pure sensory, ataxic, and pharyngeal-cervical-brachial (Wicklein *et al.*, 1997;

van den Berg *et al.*, 2014; Wakerley *et al.*, 2014; Willison *et al.*, 2016).

Local treating physicians registered clinical fluctuations. We additionally checked the data for fluctuations defined as a deterioration in MRC sum score >5 points and/or a deterioration on the GBS disability scale $\geqslant 1$ point(s) during two consecutive visits, not caused by non-GBS related complications, within the first year of follow-up. A deterioration on the GBS disability scale from 0 ('a healthy state') to 1 ('minor symptoms') was not considered a fluctuation. When MRC sum score, GBS disability score and information on clinical fluctuations were missing for two or more consecutive visits, the occurrence of a fluctuation was considered undeterminable.

When patients received multiple immunomodulating treatments (i.e. combinations of IVIg and plasma exchange), we used the first administered therapy for the treatment analysis.

The primary endpoints for clinical outcome were the ability to walk independently (GBS disability score $\leqslant 2$) at 6 and 12 months. Patients who were lost to follow-up at or after 26 and 52 weeks, or who had a missed visit and were able to walk independently at the previous visit, were considered to have reached this endpoint.

Geographical regions

To determine geographical influence on the variation of GBS, we subdivided patients into three different regions: 'Europe/Americas' (including Argentina, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Spain, The Netherlands, UK, and USA), 'Asia' (including Japan, Malaysia, and Taiwan), and 'Bangladesh'. These regions were based on previously reported prevalences of clinical variants and electrophysiological subtypes of GBS, national income level (World Bank, 2017), availability or affordability of specific immunotherapy with standard of supportive care, and geographical location of the participating countries. Europe and Americas were initially considered two separate regions based on their geographical location, but were later combined because of great similarity of the other determinative variables. The Asian group consisted only of high-income countries with good quality medical services and availability of treatment. For this study, we excluded patients from Africa ($n = 11$) and Australia ($n = 4$) from the geographical analysis because of small patient numbers.

Statistical analysis

We used SPSS Statistics 21.0 for data analysis. Continuous data are presented as medians with interquartile ranges (IQR) and dichotomized or categorical data as numbers and proportions. We used the Mann-Whitney U-test and Kruskal-Wallis test to compare continuous data, and the χ^2-test or Fisher's exact test to compare proportions. Kaplan-Meier analysis was used to present the proportion of participants able to walk independently during follow-up. A two-sided P-value < 0.05 was considered significant. P-values reflect comparisons of the three regions, unless stated otherwise.

Data availability

Data collected in IGOS will be used initially for planned research projects conducted by the IGOS Consortium. Some data will be made available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

Results

We excluded 62 (6%) patients from analysis because of alternative diagnosis: acute onset chronic inflammatory demyelinating polyneuropathy ($n = 37$), other peripheral neuropathy ($n = 8$), CNS disorder ($n = 12$), functional disorder ($n = 2$), or disorder not specified ($n = 3$). We excluded five patients because of protocol violations, and eight patients because of insufficient data. The remaining cohort of 925 patients originated from Argentina ($n = 43$), Australia ($n = 4$), Bangladesh ($n = 125$), Belgium ($n = 16$), Canada ($n = 25$), Denmark ($n = 76$), France ($n = 27$), Germany ($n = 45$), Greece ($n = 4$), Italy ($n = 82$), Japan ($n = 36$), Malaysia ($n = 28$), The Netherlands ($n = 67$), South Africa ($n = 11$), Spain ($n = 76$), Taiwan ($n = 5$), UK ($n = 129$), and USA ($n = 126$). At 1 year, 143 (16%) patients were lost to follow-up.

Cohort description and heterogeneity of GBS

GBS occurred in all age categories with an overall median age of 51 years (IQR 33–64, range 6 months to 88 years) (Fig. 1). The number of patients increased with age and reached its peak at the age categories of 50–59 and 60–69 years. Males predominated in all age categories with an overall male to female ratio of 1.5.

An antecedent event in the 4 weeks before neurological onset was reported in 649 (76%) patients, mainly upper respiratory tract infections (35%) and gastroenteritis (27%). At study entry, 677 (73%) patients had tetraparesis, 105 (11%) had paraparesis, and 19 (2%) had upper limb weakness only. During follow-up, 22 (21%) patients who presented with paraparesis and three (16%) patients who presented with sole weakness of upper limbs also developed tetraparesis. Only five patients had asymmetrical limb weakness.

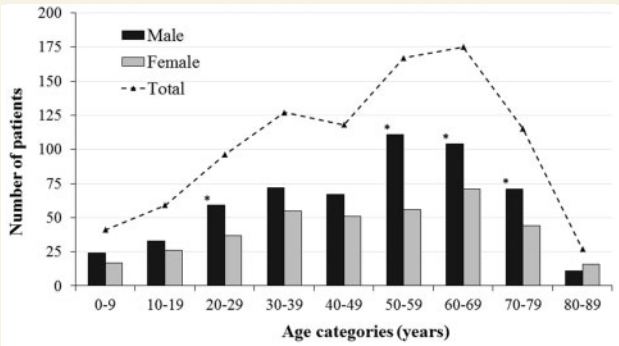

Figure 1 Age and gender distribution of IGOS cohort.
*$P < 0.05$ for difference in number of males and females per age category. $n = 919$.

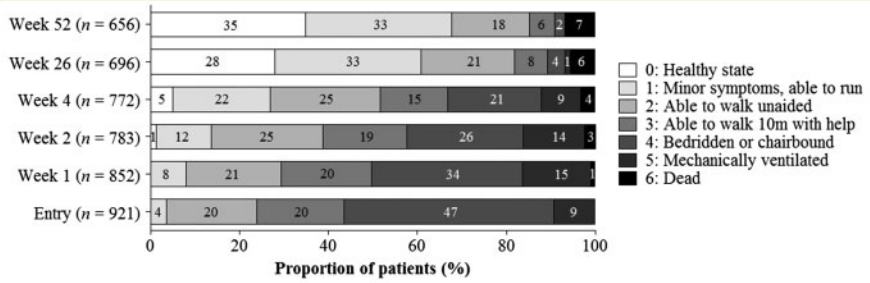

Figure 2 Clinical course during 1-year follow-up.

The median time from onset of symptoms to study entry was 6 days (IQR 3–9). Nadir was reached within 2 weeks in 824 (96%) patients, and within 4 weeks in 858 (99.8%) patients. One patient continued to deteriorate until Week 8 and another until Week 13. At nadir, the median MRC sum score was 44 (IQR 25–53), which was 2 points lower than at entry (46, IQR 33–54) (Wilcoxon signed ranks test $P < 0.001$).

The clinical course defined by the GBS disability score was highly variable (Fig. 2). For those unable to walk independently at nadir, 439 (77%) regained the ability to walk independently at 6 months, and 445 (81%) at 12 months. Overall, 19% required mechanical ventilation during the disease course. Seven per cent died during follow-up, and the median time from onset of weakness to death was 33 days (IQR 16–88, range 6–280) (Table 1).

CSF was examined in 823 (89%) patients within a median time of 4 days (IQR 2–8) from onset of neurological symptoms. Elevated CSF protein level was detected in 561 (68%) of these patients. The CSF protein level was strongly influenced by the timing of the lumbar puncture: only 50% had an elevated CSF protein level when tested within 3 days from onset of neurological symptoms, compared to 84% when tested after 7 days. Median CSF protein level in the early group was 0.45 g/l (IQR 0.33–0.73), and in the late group 0.98 g/l (IQR 0.59–1.84) ($P < 0.001$). Most patients had a normal CSF leucocyte count (<5 cells/μl) ($n = 641$, 80%). A mildly elevated cell count (5–50/μl) was found in 149 (19%) patients, but 14 (2%) patients had more than 50 leucocytes/μl (range 53–232). No alternative diagnosis was found during follow-up in these patients with CSF pleiocytosis (>50 μl) despite extensive diagnostic work-up. Six (43%) of these patients required mechanical ventilation, compared to 148 of 790 (19%) patients without pleiocytosis ($P = 0.035$), but the clinical course and outcome were similar between the two groups. Cytoalbuminological dissociation was present in 538 (67%) patients.

A nerve conduction study was performed in 829/862 (96%) patients, median 7 days (IQR 4–11) from onset of weakness. In 84 (10%) of these patients, the NCS could not be evaluated because of missing raw data or missing local reference values. NCS of the remaining 745 patients were classified as demyelinating ($n = 390$, 52%), axonal ($n = 71$, 10%), inexcitable ($n = 20$, 3%), equivocal ($n = 215$, 29%), or normal ($n = 49$, 7%). Compared to the demyelinating group, patients with axonal GBS were younger (31 years, IQR 20–56 versus 54 years, IQR 36–67; $P < 0.001$) and more often reported preceding diarrhoea (24/71, 34% versus 85/390, 22%; $P = 0.03$). Furthermore, patients with axonal GBS had more severe limb weakness at both study entry (MRC sum score 33, IQR 14–44 versus 46, IQR 34–54; $P < 0.001$) and nadir (19, IQR 5–41 versus 42, IQR 24–51; $P < 0.001$). At 6 months, 31/50 (62%) patients with axonal neuropathy were able to walk independently, versus 216/262 (82%) in the demyelinating group ($P = 0.001$). At 12 months, 34/47 (72%) with axonal GBS and 220/252 (87%) with demyelinating GBS were able to walk independently ($P = 0.01$).

Geographical variation of GBS

The demography, antecedent events, clinical presentation, electrophysiological subtypes, diagnostic findings, treatment and outcome of GBS were compared between 'Europe/Americas' ($n = 715$), 'Asia' ($n = 69$), and 'Bangladesh' ($n = 125$) (Tables 2, 3, Figs 3A, B, 4 and Supplementary Table 1).

Patients from Bangladesh were significantly younger (age 28 years, IQR 16–40) than patients from Europe/Americas (55 years, IQR 37–67, $P < 0.001$) and Asia (50 years, IQR 34–60, $P < 0.001$). An upper respiratory tract infection was the most common reported antecedent event in Europe/Americas (38%) and Asia (51%), whereas in Bangladesh, gastroenteritis was predominant (36%). Patients from Bangladesh had more severe muscle weakness than patients from the other two regions at study entry and nadir. Sensory deficits were more frequent in patients from Europe/Americas than in patients from the other two regions. Cranial nerve involvement was more frequent in patients from Asia and Bangladesh than in patients from Europe/Americas. In Asia, more patients had oculomotor weakness, whereas in Bangladesh the proportion of patients with bulbar weakness was significantly higher than in the other regions.

Patients from Asia reported pain less frequently than patients from Europe/Americas and Bangladesh. Seventy-seven (62%) of 125 patients from Bangladesh reported pain at study entry, of whom 73 (95%) had either

Table 1 Demographics and clinical features of IGOS cohort (*n* = 925)

Demographics	
Age, years (IQR)	51 (33–64)
Male:female ratio	552/373 (1.48)
Clinical features at entry	
Antecedent events (%)	
URTI	303/857 (35)
Gastroenteritis	229/857 (27)
Other[a]	117/857 (14)
None	208/857 (24)
Severity and distribution of weakness (%)	
MRC sum score, possible range 0–60[b] (IQR)	46 (32–54)
Tetraparesis	677/924 (73)
Weakness lower limbs only	105/924 (11)
Weakness upper limbs only	19/924 (2)
Unilateral limb weakness	10/924 (1)
Other[c]	15/924 (2)
No limb weakness	98/924 (11)
Sensory deficits (%)	543/890 (59)
Cranial nerve involvement (%)	464/922 (50)
Oculomotor weakness	139/922 (15)
Facial weakness	286/922 (31)
Bulbar weakness	234/922 (25)
Reflexes upper limbs[d] (%)	
Areflexia	541/920 (59)
Hyporeflexia	259/920 (28)
Normoreflexia	108/920 (12)
Hyperreflexia	12/920 (1)
Reflexes lower limbs[d] (%)	
Areflexia	704/920 (77)
Hyporeflexia	182/920 (20)
Normoreflexia	18/920 (2)
Hyperreflexia	16/920 (2)
Autonomic dysfunction (%)	228/924 (25)
Pain (%)	506/923 (55)
Time from onset of weakness to admission, days (IQR)	3 (2–6)
Clinical features at nadir	
Severity and distribution of weakness (%)	
MRC sum score, possible range 0–60[b] (IQR)	44 (25–53)
Tetraparesis	629/816 (77)
Weakness lower limbs only	82/816 (10)
Weakness upper limbs only	16/816 (2)
Unilateral limb weakness	8/816 (1)
Other[c]	11/816 (1)
No limb weakness	70/816 (9)
GBS disability score (%)	
Healthy, 0	1/815 (0.1)
Minor symptoms but able to run, 1	27/815 (3)
Able to walk independently, unable to run, 2	144/815 (18)
Not able to walk independently for at least 10 m, 3	159/815 (20)
Bedridden or wheelchair bound, 4	359/815 (44)
Mechanically ventilated for at least part of the day, 5	125/815 (15)
Clinical course	
GBS variant after 2-week follow-up (%)	
Sensorimotor	453/744 (61)
Pure motor	170/744 (23)
MFS	40/744 (5)
MFS-GBS overlap	39/744 (5)
Other[e]	42/744 (6)
Fluctuations in clinical course[f] (%)	
Monophasic course	615/700 (88)
Fluctuations during first 8 weeks	60/700 (9)
Fluctuations after first 8 weeks	16/700 (2)
Fluctuations during and after first 8 weeks	9/700 (1)
Ventilator dependency (%)	176/925 (19)
Mortality (%)	44/659 (7)

Data are presented as *n* (%) or median (IQR). URTI = upper respiratory tract infection.
[a]Other antecedent events: urinary tract infection, vaccination, surgery and other.
[b]Larger score indicates greater muscle strength.
[c]Other patterns of weakness (e.g. asymmetrical weakness).
[d]Reflexes in both paretic/paralytic and normal strength limbs.
[e]Other clinical variants: pharyngo-cervical-brachial, pure sensory, ataxic or other variant.
[f]Fluctuations defined as a decrease in the MRC sum score of >5 points and/or an increase in the GBS disability score of $\geqslant 1$ points, excluding fluctuations caused by complications not related to GBS (e.g. fractures, shin splint (medial tibial stress syndrome), pain, etc.). Changes in GBS disability score from 0 to 1 were not included.

muscle or joint pain, also including patients with a pure motor variant. Patients from Europe/Americas were less frequently ventilated (17%) than patients from Asia (25%, $P = 0.13$) and Bangladesh (29%, $P = 0.003$).

The predominant clinical pattern of GBS in Europe/Americas and Asia was sensorimotor (Europe/Americas: $n = 387$, 69%; Asia $n = 27$, 43%), whereas in Bangladesh most patients had pure motor GBS ($n = 74$, 69%). MFS or MFS-GBS overlap occurred more frequently in Asia ($n = 14$, 22%) than in Europe/Americas ($n = 57$, 11%) and Bangladesh ($n = 1$, 1%) ($P < 0.001$).

Considerable variation was observed in treatment of GBS between regions. IVIg was the most common treatment for patients from Europe/Americas ($n = 612$, 86%) and Asia ($n = 50$, 73%), whereas in Bangladesh the majority of patients ($n = 108$, 86%) received no immunomodulating therapy.

The median time to regain the ability to walk independently was 63 days (IQR 28–186) in Europe/Americas, 39 days (IQR 17–94) in Asia, and 95 days (IQR 36–190) in Bangladesh ($P = 0.002$). The proportion of patients who regained the ability to walk independently after 12 months follow-up was 69% in Bangladesh, 83% in Europe/Americas, and 91% in Asia ($P = 0.003$; Tables 2, 3 and Fig. 4). Mortality was significantly higher in Bangladesh ($n = 19$, 17%) than in Europe/Americas ($n = 23$, 5%, $P < 0.001$) and Asia ($n = 1$, 2%, $P = 0.02$).

The predominant electrophysiological subtype was demyelinating for all regions (Europe/Americas: $n = 312$, 55%; Asia: $n = 29$, 45%; Bangladesh: $n = 38$, 40%). The axonal subtype occurred more often in Bangladesh ($n = 34$, 36%). Clinical differences among electrophysiological subtypes were compared for each region (Supplementary Table 2). In all three regions, patients with the axonal subtype

Table 2 Differences in GBS between geographical regions

	Region			
	Europe/Americas (*n* = 715)	Asia (*n* = 69)	Bangladesh (*n* = 125)	*P*-value
Demographics				
Age, years (IQR)	55 (37–67)	50 (34–60)	28 (16–40)	**<0.001**
Male/female ratio (%)	418/297 (1.41)	42/27 (1.56)	84/41 (2.05)	0.18
Clinical features at entry				
MRC sum score, possible range 0–60[a] (IQR)	48 (38–56)	49 (40–58)	22 (7–37)	**<0.001**
Sensory deficits (%)	463/686 (65)	37/68 (54)	35/120 (28)	**<0.001**
Cranial nerve involvement (%)	330/712 (46)	44/69 (64)	84/125 (67)	**<0.001**
Oculomotor weakness	106/712 (15)	26/69 (38)	5/125 (4)	**<0.001**
Facial weakness	220/712 (31)	28/69 (41)	32/125 (26)	0.10
Bulbar weakness	142/712 (20)	23/69 (33)	64/125 (51)	**<0.001**
Autonomic dysfunction (%)	189/714 (27)	7/69 (10)	28/125 (22)	**0.01**
Pain (%)	415/713 (58)	8/69 (12)	77/125 (62)	**<0.001**
Time from onset of weakness to admission, days (IQR)	3 (2–6)	4 (2–6)	4 (2–8)	**0.01**
Clinical features at nadir				
MRC sum score, possible range 0–60[a] (IQR)	46 (30–54)	48 (34–58)	16 (3–32)	**<0.001**
GBS disability score (%)				
Unable to walk independently (>2)	478/626 (76)	50/66 (76)	100/107 (93)	**<0.001**
Sensory deficits (%)	408/588 (69)	37/63 (59)	29/100 (29)	**<0.001**
Cranial nerve involvement (%)	304/620 (49)	44/65 (68)	73/107 (68)	**<0.001**
Oculomotor weakness	84/620 (14)	25/65 (39)	5/107 (5)	**<0.001**
Facial weakness	220/620 (36)	31/65 (48)	32/107 (30)	0.06
Bulbar weakness	136/620 (22)	24/65 (37)	57/107 (53)	**<0.001**
Autonomic dysfunction (%)	184/626 (29)	11/66 (17)	30/107 (28)	0.09
Pain (%)	354/625 (57)	11/66 (17)	67/107 (63)	**<0.001**
Ventilator dependency (%)	121/715 (17)	17/69 (25)	36/125 (29)	**0.004**
Electrophysiology classification (%)				
Demyelinating	312/573 (55)	29/65 (45)	38/94 (40)	**0.02**
Axonal	33/573 (6)	4/65 (6)	34/94 (36)	**<0.001**
Inexcitable	10/573 (2)	1/65 (2)	9/94 (10)	**<0.001**
Equivocal	182/573 (32)	20/65 (31)	12/94 (10)	**0.001**
Normal	36/573 (6)	11/65 (17)	1/94 (1)	**<0.001**
Initial treatment (%)				
None	54/715 (7)	9/69 (13)	108/125 (86)	**<0.001**
IVIg	612/715 (86)	50/69 (73)	7/125 (6)	**<0.001**
PE	43/715 (6)	10/69 (15)	9/125 (7)	**0.03**
Other[b]	6/715 (1)	0/69 (0)	1/125 (1)	0.75
Time from onset of weakness to treatment, days (IQR)	4 (2–7)	5 (3–7)	7 (5–12)	**0.003**
Outcome				
Median time to independent walking, days (IQR)	63 (28–186)	39 (17–94)	95 (36–190)	**0.002**
Able to walk independently at 6 months (%)	331/418 (79)	36/41 (88)	60/97 (62)	**<0.001**
Able to walk independently at 12 months (%)	334/404 (83)	31/34 (91)	67/97 (69)	**0.003**
Mortality				
Patients deceased at 12 months (%)	23/486 (5)	1/45 (2)	19/114 (17)	**<0.001**

Data are presented as *n* (%) or median (IQR). *P*-values represent a comparison between the three regions. *P*-values below 0.05 are highlighted in bold. PE = plasma exchange.
[a]Larger score indicates greater muscle strength.
[b]Other treatment: steroids, immunoadsorption and trial medication.

were younger than patients with the demyelinating subtype. Sensory deficits at entry and nadir were less frequent in patients with axonal neuropathy. There was a trend towards a lower MRC sum score at study entry and nadir (only significant for Europe/Americas), and poorer outcome at 6 and 12 months in the axonal groups compared to the demyelinating groups (Supplementary Table 2).

Discussion

Our study demonstrates the marked worldwide variation of GBS with respect to clinical variants, severity, electrophysiological subtypes, and outcome. This variation is influenced by regional differences in demography, preceding events, and treatment.

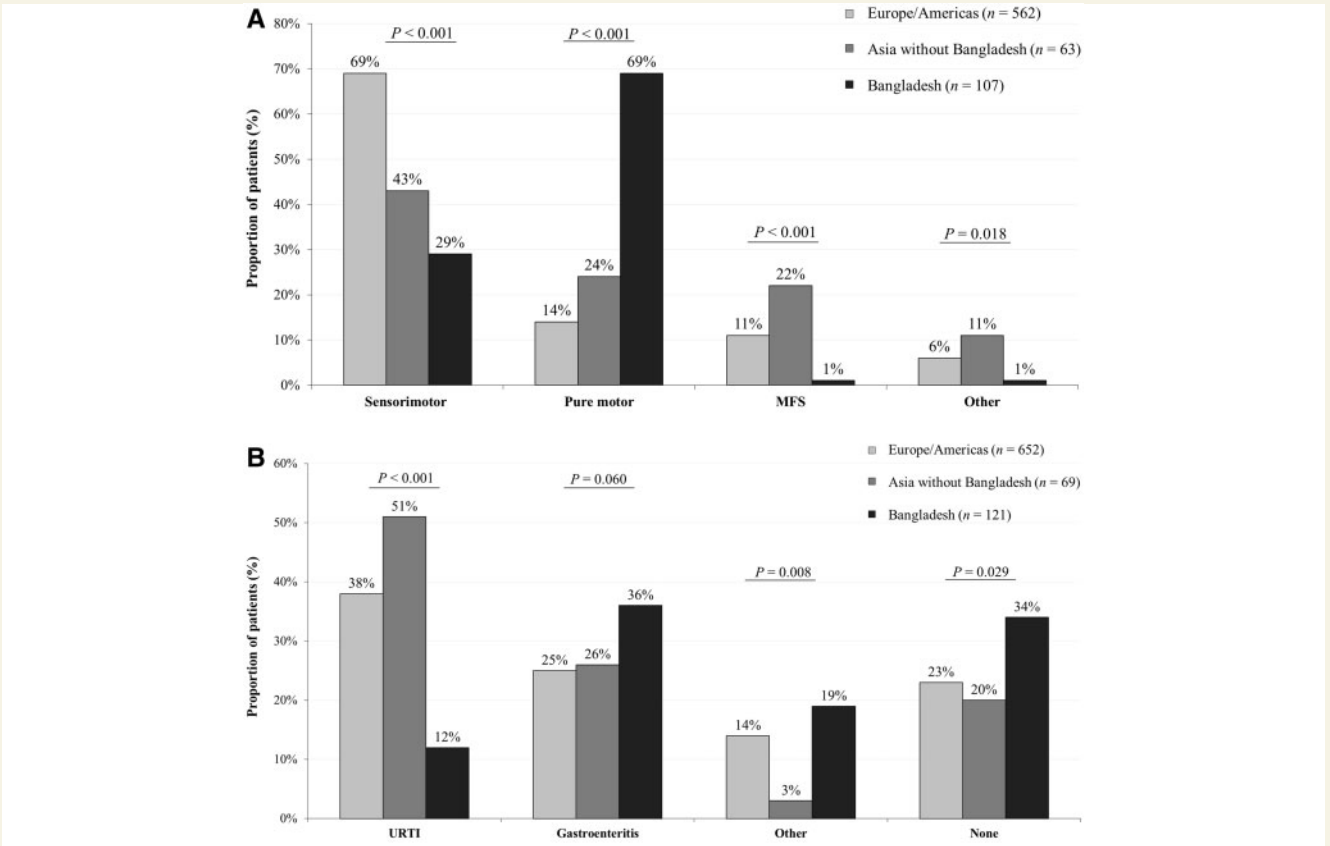

Figure 3 Clinical variants (Week 2) (A) and antecedent events (B) in different geographical areas. (**A**) MFS: Miller Fisher and Miller Fisher GBS overlap syndromes. Other: pharyngeal-cervical-brachial, pure sensory, ataxic and other clinical variants. (**B**) Other: urinary tract infection, vaccination, surgery and other antecedent events. URTI = upper respiratory tract infection.

In all three regions, the frequency of GBS increased with age, for both males and females. Similar age distributions for GBS have been found previously (McGrogan *et al.*, 2009; Sejvar *et al.*, 2011*a*). Patients from Bangladesh were younger than patients from the other two regions, which corresponds to results from a previous study in Bangladesh, where the median age was 21 years (range 2–65) (Islam *et al.*, 2010). The regional differences in age distribution may be explained by the variation in demography of the general populations and merely reflect the relative number of persons at risk in each age category per region (UN, http://data.un.org). Males were more frequently affected than females in a ratio of 1.5:1, in all age categories and regions. Similar male to female ratios have been reported previously (Hughes and Cornblath, 2005; van den Berg *et al.*, 2014). Therefore, male gender and higher age are independent risk factors for developing GBS worldwide.

The full clinical spectrum of GBS was observed in patients from all countries participating in IGOS, but the frequency of variants differed considerably between regions. The predominant variant in Europe/Americas was sensorimotor, whereas in Bangladesh pure motor GBS predominated. The proportion of patients with MFS or MFS-GBS overlap syndrome was higher in Asia than in the other two regions. A similar distribution of clinical variants per region has been suggested in previous reports from single countries. In these studies, the frequency of pure motor GBS ranged from 10–18% in Europe (Visser *et al.*, 1995) to as high as 92% in Bangladesh (Islam *et al.*, 2010). The frequency of MFS varied from 3% in Europe (Lo, 2007) to 34% in Eastern Asia (Mori *et al.*, 2001; Mitsui *et al.*, 2015). The clinical presentation of the patients in the IGOS cohort was similar to previous studies from single countries in Europe/Americas (Fokke *et al.*, 2014), Asia (Matsui *et al.*, 2018) and Bangladesh (Islam *et al.*, 2016; Ishaque *et al.*, 2017).

Almost all patients reached nadir within 4 weeks after study entry (99.8%), and 96% of patients even within 2 weeks. In another study, 3% of the patients reached nadir between 4 and 6 weeks (Fokke *et al.*, 2014). While a progressive phase of more than 4 weeks could be regarded as an exception, subacute inflammatory demyelinating polyradiculoneuropathy should be considered in these patients, a previously described intermediate form between GBS and chronic inflammatory demyelinating polyradiculoneuropathy (Hughes *et al.*, 1992). At the other end of the GBS spectrum, patients reached clinical nadir within days.

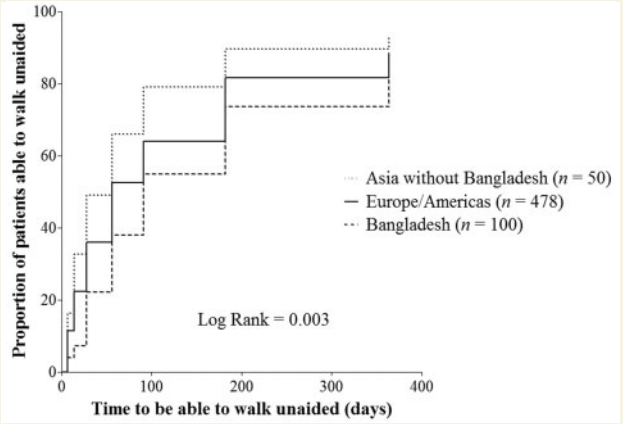

Figure 4 Kaplan-Meier analysis of time to walk unaided in different geographical areas. Kaplan-Meier analysis for patients unable to walk unaided (GBS disability score > 2) at disease nadir.

Table 3 Kaplan-Meier analysis: numbers at risk

	Numbers at risk at different time points (days)					
	7	14	28	56	91	182
Europe/Americas	416	360	285	198	139	57
Asia	41	33	24	13	6	3
Bangladesh	92	81	64	51	34	19

Some patients already had inexcitable nerves at first NCS. The mechanism of nerve inexcitability is unknown but may be mediated by early loss of axonal or myelin structural integrity or by functional block at the nodes of Ranvier or nerve terminals, caused by anti-nerve antibodies, ionic imbalance, or other inflammatory mediators.

Demyelinating and axonal subtypes of GBS were seen in all participating countries but the frequencies varied between regions. The demyelinating subtype was the predominant subtype in all regions. However, in Bangladesh a substantial proportion of patients had axonal neuropathy. These findings are in line with results from previous studies, where demyelinating GBS was found in 60–80% of North American and European patients (Hadden *et al.*, 1998; van den Berg *et al.*, 2014). Axonal GBS was reported in 3–17% in Europe (Hadden *et al.*, 1998; Sekiguchi *et al.*, 2012; Kuwabara and Yuki, 2013), in 23–65% in Asia (Kuwabara and Yuki, 2013; Mitsui *et al.*, 2015), and up to 67% in Bangladesh (Islam *et al.*, 2010). Interestingly, in all three regions patients with axonal GBS were younger than patients with demyelinating GBS. The influence of electrophysiological subtype on prognosis is under debate, as recovery in axonal GBS can be slow and incomplete due to axonal degeneration, or faster due to resolving transient conduction blocks, and may depend upon the subtype criteria (Kuwabara and Yuki, 2013; van den Berg *et al.*, 2014). The current study showed that the axonal subtype was significantly associated with poor recovery in the full cohort and a similar trend was observed in the subgroup analysis per region (Supplementary Table 2). The association between axonal GBS and younger age may reduce the effect of axonal involvement on poor recovery. Further analysis of NCS and other prognostic factors is required to determine the association between GBS subtype and outcome.

The regional differences in frequencies of clinical and electrophysiological subforms of GBS may be explained in part by the variation in local exposure to infections. The frequency of patient-reported gastroenteritis in our cohort ranged from 25% in Europe/Americas to 36% in Bangladesh. Previous studies have shown an association between preceding gastroenteritis and pure motor and axonal GBS (Islam *et al.*, 2010; Kuwabara and Yuki, 2013). *Campylobacter jejuni* is the predominant cause of gastroenteritis preceding GBS worldwide, but previous reports suggest that the frequency of this infection may differ substantially among regions. The association between preceding *C. jejuni* infection and axonal GBS is related to the induction of cross-reactive antibodies to gangliosides (Willison *et al.*, 2016). A recent retrospective study indicated a relatively high frequency of the demyelinating subtype (49%) and lower frequency of the axonal subtype (19%) in Southern China (Liu *et al.*, 2018), while previous studies from Northern China from the 1990s reported the axonal subtype in 65% of GBS patients (Ho *et al.*, 1995). It is unknown whether this variation represents a regional difference within China or a change in GBS spectrum over time in parallel to changes in exposure to infections, especially with *C. jejuni* (Baker *et al.*, 2012; Liu *et al.*, 2018). Future serological studies will investigate the role of preceding infections, and immune responses to these infections, to explain the regional differences.

The clinical course and outcome varied substantially among the three regions. The best outcome was observed in Asia, in part related to the higher frequency of MFS in that region (Mori *et al.*, 2001; Mitsui *et al.*, 2015). The worst outcome was found in Bangladesh, despite the younger age of these patients. Several factors previously associated with poor prognosis were more frequent in Bangladesh, such as the frequency of preceding gastroenteritis, axonal subtype, and more severe disease in the acute stage. Most importantly, only 13% of the patients in Bangladesh received plasma exchange or IVIg and the facilities for supportive care were limited.

Although this study is the largest prospective study on GBS so far, there are several limitations. First, IGOS aimed to include the full spectrum of GBS, irrespective of age, disease severity, and treatment, but referral bias probably favoured inclusion of patients with more severe disease that required hospitalization and treatment. Participating centres were mostly tertiary care hospitals with specific neuromuscular expertise. It is unknown

whether referral bias differed among countries and if this might have influenced the observed regional differences. Second, the number of inclusions varied per country and several areas, especially Asia, Africa, and Australia, were under-represented. The centre in Dhaka, Bangladesh, in contrast, is the national and public tertiary care hospital for GBS, which explains the high number of inclusions and the high proportion of patients receiving supportive care only (Islam *et al.*, 2010, 2016; Ishaque *et al.*, 2017). Third, although IGOS included 1000 patients, the numbers in some subgroups were small and their analyses had limited power. Enrolment of patients in IGOS is continuing to overcome this problem. Lastly, patients were classified according to only one set of electrophysiological criteria using a single NCS, while the assigned GBS subtype depends on the criteria used and may change during follow-up. The electrophysiology of GBS and performance of different sets for classification will be evaluated in future dedicated studies.

The standardized collection of data in IGOS has enabled us to identify differences in the preceding factors, clinical presentation, neurophysiological classification and course of GBS between regions. In combination with the biosamples collected at the same time, this information will improve understanding of pathogenesis—involving identification of risk factors for GBS, including preceding infections of which some may be preventable—and allow better prognostic modelling, adapted to different parts of the world.

Acknowledgements

We thank the patients who participated in this long term follow up study. We also thank Melissa Mandarakas for her contribution to the manuscript, Esmee Venema for her input into the statistical analyses, and Judith Drenthen for her support with classifying the nerve conduction studies.

Funding

This study is funded by GBS-CIDP Foundation International, gain, Erasmus University Medical Centre, Glasgow University, CSL Behring, Grifols and Annexon.

Competing interests

D.R.C is a consultant for Acetylon, Alcobra Pharma, Alnylam Pharmaceuticals, Annexon Biosciences, Akros Pharma, Biotest Pharmaceuticals, Boehringer Ingelheim, Cigna Health Management, CSL Behring, DP Clinical, Grifols, Hansa Medical, Karos Pharmaceuticals, Neurocrine Biosciences, Novartis, Octapharma, Pharnext, Seattle Genetics, Sun Pharmaceuticals, and Syntimmune. He is on the data and safety monitoring board for Sanofi, Pledpharma, Pfizer, Johnson & Johnson, Ionis Pharmaceuticals, GlaxoSmithKline, and Axovant Sciences. He has licensed technology for the Total Neuropathy Score for Acetylon, AstraZeneca, Calithera Biosciences, Genentech, Neurocrine Biosciences, Merrimack Pharmaceuticals, Seattle Genetics, and Shire Development Inc. He is on the Board of Directors for the Peripheral Nerve Society. G.C. received a honorarium from CSL Behring. P.A.v.D has received honoraria for consulting, lectures and serving on steering committees from Octapharma, Kedrion, CSL Behring, Grifols, and Hansa (all honoraria to departmental research fund), and is currently receiving grants from Prinses Beatrix Spierfonds, Sanquin Blood supply, Shire and Grifols. P.A.v.D is President Elect of the Peripheral Nerve Society, member of the Inflammatory Neuropathy Consortium, Medical Advisory Board for the GBS-CIDP Foundation International, editorial board for the Journal of the Neurological Sciences and Journal of Neuromuscular Diseases. He is PI of the RCT investigating the effect of methylprednisolone in GBS (MP/IVIg RCT in GBS) and the RCT investigating the effect of a second dose IVIg in GBS (SID-GBS study). H.P.H received fees for consulting, serving on steering committees and speaking at symposia from Baxter, CSL Behring, Novartis and Octapharma related to work on chronic immune neuropathies. R.A.C.H has current consultancies with LFB and former consultancies with Novartis. S.K. received a research grant from Teijin, Japan Blood Products Organization, and Japan Pharmaceutical, and speech honoraria from Teijin, Japan Blood Products Organization, and Japan Pharmaceutical. E.N-O. received personal fees for lecturing or Advisory/Scientific/Safety Board Membership not related to this study from Baxter, Italy; CSL Behring, Switzerland; Kedrion Biopharma, Italy; LFB, France; Novartis, Switzerland; UCB, UK; Astellas Biopharma, the Netherlands. L.Q. has received research grants from the Instituto de Salud Carlos III, Spain and FEDER (grant FIS16/00627), has provided expert testimony for Grifols and CSL Behring and received research funds from Novartis Spain and Grifols (Spin Award). S.W.R. received funds over the last 5 years including, but not limited to, travel support, honoraria, trial payments, research and clinical support to the neurology department of which he is a member, from bodies and charities: NHMRC, NIH, USMDA, NSWMDA, MGANSW, MGAQLD, MAA, Beeren foundation, anonymous donors; and from pharmaceutical / biological companies: Aspreva, Baxter, Bayer Schering, Biogen Idec, CSL, Genzyme, Grifols, Merck, Novartis, Sanofi Aventis Genzyme, Servier, TEVA. He is co-founder/shareholder of Medical Safety Systems (grant and contracts with Genzyme $>$\$25 000 AUD including a per patient payment, potential application to multiple drugs), part of the national IVIG Governance Advisory Council & Specialist Working Group Australia (Neurology) (paid), the Australian Technical Advisory Group on Immunisation Varicella Zoster working party (unpaid), and board member of the Nerve Research Foundation (unpaid). S.W.R receives public salary as a staff specialist neurologist from Sydney Local Health District (paid), private billings from patients and Medicare

Australia reimbursement as a private practice neurologist (paid), and he is medical advisor (unpaid) to various patient and advocacy groups. B.C.J. is currently receiving funding for research projects from Prinses Beatrix Spierfonds, Horizon 2020, GBS-CIDP Foundation International, Grifols, CSL Behring and Annexon. He is on the Medical Advisory Board for the GBS-CIDP Foundation International, and a member of the Inflammatory Neuropathy Consortium.

Supplementary material

Supplementary material is available at *Brain* online.

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Appendix 1

Full details can be found in the Supplementary material.

IGOS Consortium

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