Journal of Neurology (2019) 266:440–449
https://doi.org/10.1007/s00415-018-9151-x

ORIGINAL COMMUNICATION

Guillain–Barré syndrome in Denmark: a population-based study on epidemiology, diagnosis and clinical severity

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Received: 14 October 2018 / Revised: 4 December 2018 / Accepted: 5 December 2018 / Published online: 7 December 2018

Abstract

Objectives To describe the epidemiology and clinical heterogeneity of Guillain–Barré syndrome (GBS) in Denmark and to compare a population-based cohort to prospectively included patients in the International GBS Outcome Study (IGOS).

Methods The incidence rate (IR) of GBS in Denmark from September 2012 to December 2015, applying the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria, was estimated and the level of diagnostic certainty was described with the Brighton criteria. All cases registered with a diagnosis of GBS or other inflammatory neuropathies in the Danish National Hospital Registry were reviewed for diagnostic criteria and for information on treatment and clinical course.

Results A total of 299 GBS cases were confirmed, corresponding to a crude IR of 1.59 (95% CI 1.42–1.78) per 100,000 per year. The Brighton criteria level 1–3 of diagnostic certainty was met in 279 (93%) of the patients. Thirty-five percent of the patients were mildly affected (GBS disability score < 3) and a correlation between high age and high disability score at nadir was found (Spearman's rank correlation coefficient 0.42, $p < 0.0001$). The group of 89 (30%) patients who were enrolled in IGOS had higher GBS disability score at nadir, were admitted 5 days earlier, reached nadir 4 days faster, and a larger proportion received treatment with IVIg (all $p < 0.05$).

Conclusion The epidemiology and full clinical spectrum of GBS are described in a population-based study. This includes a larger proportion of milder cases that are underrepresented in prospective cohorts such as IGOS.

Keywords Guillain–Barré syndrome · Epidemiology · Brighton criteria · International GBS outcome study · IGOS

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-018-9151-x) contains supplementary material, which is available to authorized users.

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Introduction

Guillain–Barré syndrome (GBS) is a rapidly progressive polyradiculoneuropathy, presenting with progressing muscle weakness and sensory symptoms. The disease course ranges from mild disease to severe disability with tetraparalysis, respiratory failure, autonomic dysfunction, and a mortality of 2–3% in developed countries [1, 2]. Recovery is accelerated with treatment with either immunoglobulins (IVIg) or plasma exchange (PE) [3, 4].

Diagnosis of GBS relies on a combination of clinical features, including bilateral and flaccid weakness of limbs, decreased or absent deep tendon reflexes, monophasic course of disease, and typical findings on cerebrospinal fluid (CSF) and nerve conduction studies (NCS) [5, 6]. Clinical variants are based on characteristic symptoms and signs as, for example, in Miller Fisher syndrome (MFS), or the pharyngeal-cervical-brachial (PCB) variant. To improve comparability of GBS studies and to standardize the diagnostic certainty in epidemiological studies, the Brighton Collaboration has developed a set of criteria with level 1–4 of diagnostic certainty. However, the Brighton criteria have only been applied to a few populations [7, 8].

Previous studies of epidemiology in GBS have used different inclusion criteria and various methods to identify cases, including discharge registers, prospective or retrospective hospital cohorts, or insurance reimbursement registers [9]. Reported incidence rates (IR) have varied accordingly. For several reasons, there are unique resources for conduction of epidemiological studies in Denmark. First, the national public healthcare system provides free medical care for all residents, including diagnosis and treatment of GBS. Second, from birth or immigration, all residents are assigned with a unique 10-digit personal registration number (CPR) in the Danish Civil Registration System. Third, the Danish National Patient Register (DNPR) contains information on all patients discharged from hospitals or outpatient clinics in Denmark since 1977. Furthermore, Denmark is a country of 5.64 million which is sufficient to describe the epidemiology of GSB with an estimated IR of 1–2 per 100,000 per year [9].

The incidence and clinical range of GBS have been described in very few population-based studies, but in several retrospective or prospective hospital-based cohorts. Knowing the true incidence and the full range of GBS variants and severities is important for designing diagnostic criteria and future trials and to estimate the impact on the health care system. The International GBS Outcome Study (IGOS) is currently the largest prospective, international study of GBS aiming to describe the disease phenotypes, clinical course, treatment and prognosis in detail. Enrolment of patients started in 2012, and Denmark has participated since September 1st, 2012. IGOS provides high-quality prospective data. However, there is no population-based control group to assess the generalizability and external validity of the findings [10].

Therefore, we conducted a Danish nationwide population-based study to estimate the IR and epidemiology of GBS, as well as to characterize patients with respect to key diagnostic findings, level of diagnostic certainty according to the Brighton criteria, clinical presentation and treatment. Finally, the national unbiased patient cohort was compared to the Danish patients included in IGOS (IGOS-DK) during the same period of time.

Methods

Study design

This nationwide population-based study included all GBS patients in contact with a public hospital in Denmark, including contacts in the emergency room, outpatient and hospital wards, from September 1st, 2012 to December 31st, 2015 (see Supplementary Table 1 for list of hospitals and departments). In the same period, a subgroup of patients from Denmark was included in the IGOS 1000 cohort [11]. Cases were identified in the DNPR with the GBS-specific International Classification of Diagnosis, 10th revision (ICD-10) registration code G61.0. In addition, we identified patients with registration codes G61.1 (serum neuropathy), G61.8 (other inflammatory neuropathy) and G61.9 (inflammatory neuropathy, unspecified) had they been admitted to neurological departments, since atypical forms of GBS may have been registered with these less specific codes. DNPR search criteria included principal, primary as well as secondary diagnoses. The study was approved by the Central Denmark Region Committees on Health Research Ethics and the Danish Data Protection Agency. Data were collected and stored anonymized according to the guidelines of the Danish Data Protection Agency.

Incidence rate

The crude IR of GBS was based on the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for GBS or one of the variants of GBS, including MFS, the PCB variant and overlap syndromes [5, 9, 12, 13]. No exclusion criteria were applied so as to be able to capture the full spectrum of GBS. The level of diagnostic certainty based on clinical and laboratory data was graded 1–4 according to the case definitions from the Brighton Collaboration [7] and the IR was based on the patients classified as Brighton level 1–3. Level 1 requires bilateral and flaccid

weakness of limbs, decreased or absent deep tendon reflexes, monophasic course of disease and time between onset–nadir 12 h–28 days, CSF cell count < 50/µL, elevated CSF protein, NCS findings consistent with GBS, and absence of alternative diagnosis. Level 2 includes the clinical criteria and CSF cell count < 50 cells/µL (with or without CSF protein elevation above laboratory normal value) or if CSF is not available, NCS consistent with GBS. Level 3 requires all the clinical features without NCS or CSF. Level 4 is a reported case of GBS with no alternative diagnosis. Other case definitions apply for MFS where ophthalmoplegia, areflexia, ataxia, absence of limb weakness, no alterations in consciousness or corticospinal tract and a monophasic illness pattern are key features, and are required for a diagnostic level of certainty of 1–3 [1, 6, 7]. The PCB variant is characterized by oropharyngeal and neck weakness as well as a bilateral arm weakness with areflexia [13].

Validation of diagnosis and classification in subtypes

Medical records from all patients were reviewed for fulfillment of the inclusion criteria (Fig. 1). If the criteria were met, data from the medical records were extracted to enable classification of diagnostic level according to the Brighton criteria. Information on age, sex, hospital department, date of admission, and mortality were readily available in the DNPR database. Further collection of data included the severity of disease using the GBS disability scale ranging from 0 to 6 [14], presence of autonomic dysfunction, pain, weakness, sensory loss, cranial nerve involvement, CSF studies, and treatment. Nadir of GBS was defined as the highest recorded GBS disability score during follow-up. If a nerve conduction study was performed within the first 28 days after onset of weakness, findings, as interpreted by the treating neurologist, were classified as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor and/or sensory axonal neuropathy (AMAN/AMSAN), unresponsive, equivocal, or normal as suggested in the Hadden criteria [15].

Definition of the clinical cohorts

To compare the clinical and key diagnostic characteristics of the population-based cohort with the prospectively included IGOS cohort, the nationwide Danish cohort was divided into two subgroups: those included in IGOS (IGOS-DK) and those not included in the IGOS (non-IGOS-DK), as indicated in Fig. 1. Data from the IGOS-DK cohort were collected according to the IGOS protocol [10].

Data analysis

Crude IR of GBS was calculated as the total number of cases per observed person-year (PY) with the mean number of inhabitants in Denmark during the study period. Age- and sex-specific IRs were calculated as the number of cases in each age category per PY and the mean number of inhabitants in the respective age and sex category. Mean population

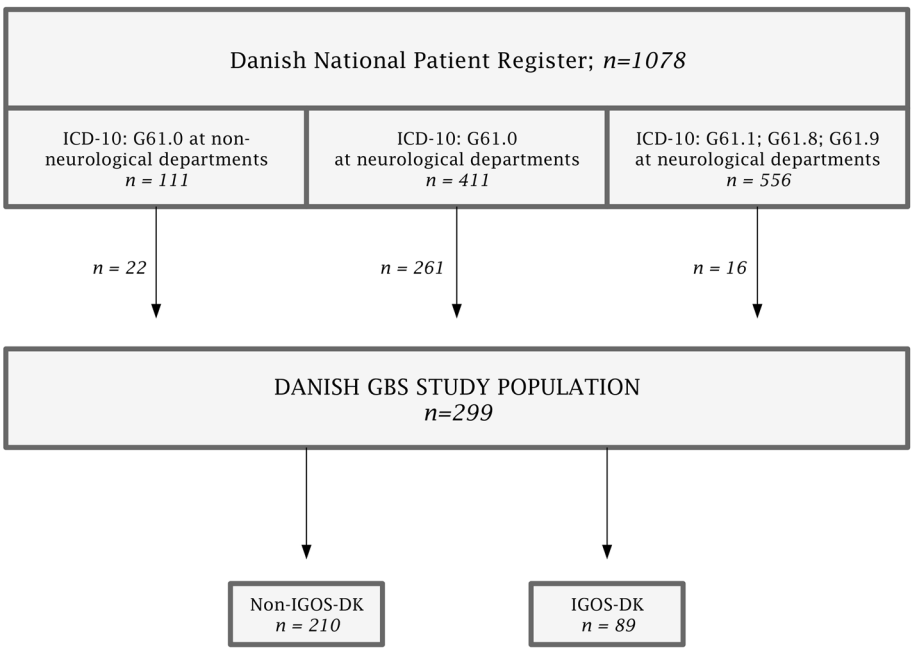

Fig. 1 Flow chart for patient selection from September 2012 to December 2015. ICD-10 codes: G61.0 (Guillain–Barré syndrome), G61.1 (serum neuropathy), G61.8 (other inflammatory neuropathies) and G61.9 (inflammatory neuropathy, unspecified)

in Denmark in the inclusion period (5,638,737) and population per category were extracted from Statbank Denmark [16].

Data were analyzed using GraphPad Prism 7 (GraphPad Software). Descriptive statistics were used for clinical scores including median and interquartile range (IQR). For normally distributed data, the *t* test was used, and for non-normally distributed data, log transformation was performed for normalization. For comparison of medians, the Mann–Whitney *U* test was applied. Proportions were compared using the Chi square test or Fisher's exact test when appropriate. The cutoff for significance in *p* value was 0.05. Spearman's rank correlation coefficient (rs) was used to evaluate correlations.

Results

Incidence rate of GBS in Denmark

In the DNPR, 1078 patients with a registered diagnosis of inflammatory neuropathy (G61.0, G61.1, G61.8, or G61.9) were identified. This included 411 (38.1%) with the GBS-specific ICD-10 code, G61.0, registered at neurological departments, 111 (10.3%) with G61.0 at other hospital departments, and 556 (51.6%) patients with a diagnostic code of G61.1, G61.8, or G61.9 (Fig. 1). Reviewing the medical records identified a total of 299 (27.7%) patients fulfilling the NINDS diagnostic criteria in the inclusion period, corresponding to a crude IR of GBS in Denmark of 1.59 per 100,000 PY (95% confidence interval (CI) 1.42–1.78). GBS patients were included from 14 different hospitals representing all five Danish regions (Fig. 2). Patients were aged 1–87 years with a median age of 55 (IQR 37–67). Figure 3 showed age- and sex-specific IRs per 100,000 PY in Denmark. IR was higher among males than females (IRR 1.39 $p = 0.01$). This difference was largest in the age groups 50–59 and 80–89 years. The IR was lowest in the age group 10–19 years (0.39 per 100,000 PY) and highest in the age group 60–69 years (2.69 per 100,000 PY). IRs increased for each age group except for a small decline in the age group 40–49 with an IR of 1.30 per 100,000 PY. There was a seasonal variation in IR with higher IR during the winter

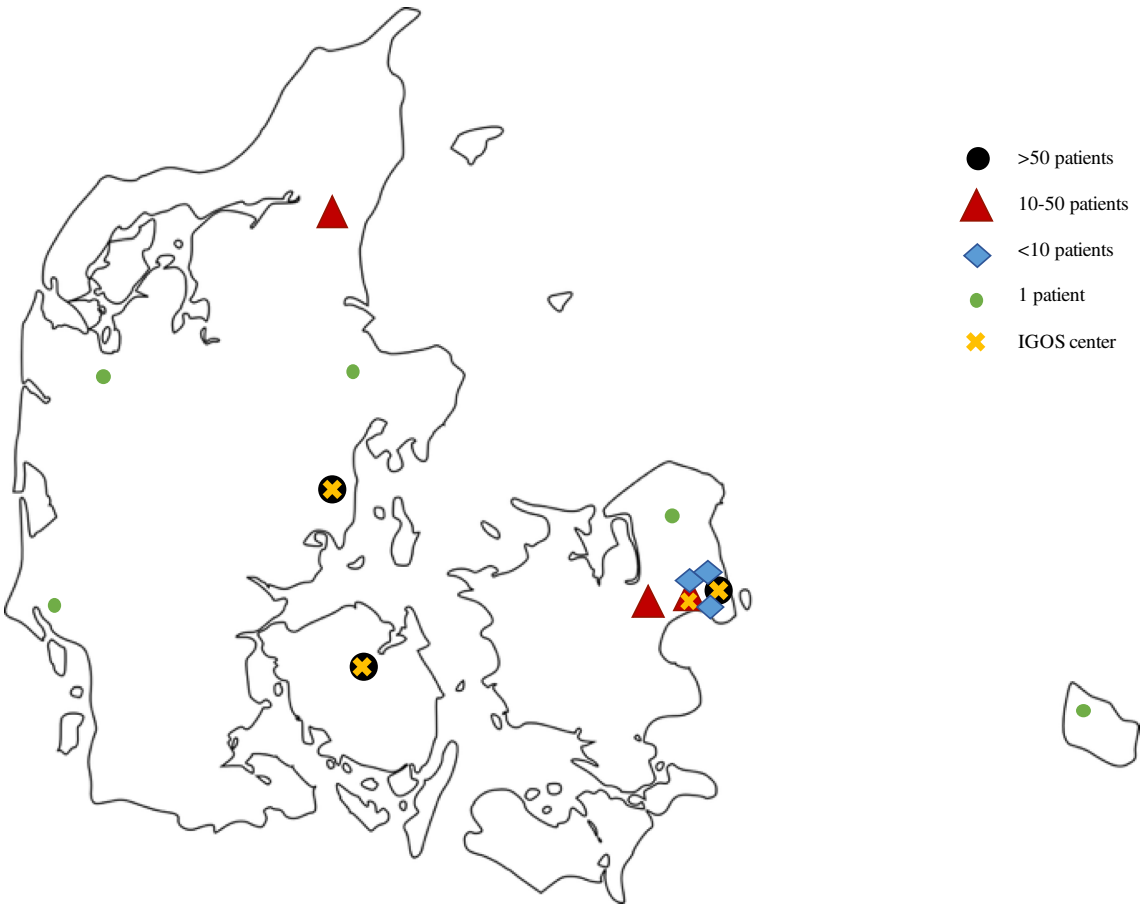

Fig. 2 Distribution of GBS patients and IGOS centers in Denmark from September 2012 to December 2015. Data available from Danish National Patient Register

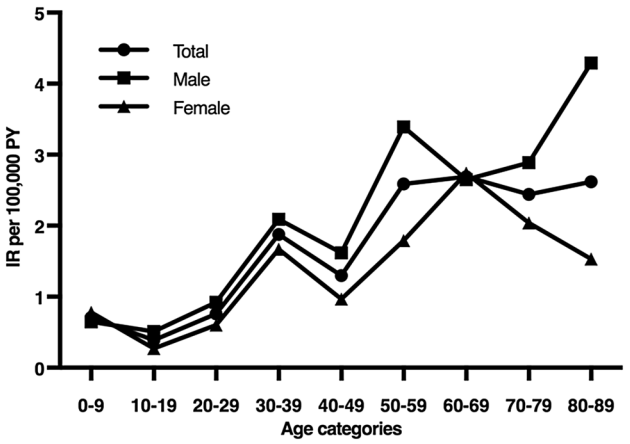

Fig. 3 Age- and gender-specific incidence rates (IR) of GBS per 100,000 persons per year (PY) in Denmark, September 2012 to December 2015. $N = 299$. IRs expressed per male/female/total population in respective age categories

half-year (October–March, IR 1.89, 95% CI 1.61–2.16) compared to the summer (April–September, IR 1.32, 95% CI 1.11–1.58) with a winter/summer IRR of 1.41, 95% CI 1.12–1.78, $p = 0.003$.

In this study cohort defined by the NINDS diagnostic criteria, 279 cases (93%) fulfilled the Brighton criteria for the diagnosis of GBS level 1–3 with a corresponding IR of 1.49 (95% CI 1.32; 1.67) (Table 1). Amongst 20 (7%) patients categorized as level four, 4 did not have hyporeflexia, 4 did not have a monophasic course of disease and 12 patients did not reach nadir within 28 days. The latter reached nadir within a median of 38 days (IQR 33–59). Compared to the patients fulfilling the level 1–3 criteria, these patients did not differ in age and sex, disability score at nadir, autonomic dysfunction, cranial nerve involvement or treatment.

Table 1 shows the clinical and laboratory characteristics of the Danish GBS cohort. The most common clinical variant of GBS was the sensorimotor form that affected 77% of patients, whereas 14% had pure motor form, 7% had MFS, 1.3% had GBS–MFS overlap syndrome, and 0.7% had PCB. There was a positive correlation between the proportion of patients with the sensorimotor form and age: rising from half of the patients aged 0–9 years to almost 90% of the patients aged 80–90 years (rs = 0.80) ($p < 0.05$). Likewise, a negative correlation was found in the pure motor form with a decrease from a third of the 0- to 9-year-olds to only 6% of the patients aged 80–89 years (rs = −0.87) ($p < 0.05$) (Fig. 4). We also saw a correlation between age and severity with an increase in age with higher disability score at nadir (rs = 0.42, $p < 0.0001$) (Fig. 5). Thus, patients with a disability score of 1 had a median age of 37 years (IQR 22–46), while patients with a disability score of 5 had a median age of 68 years (IQR 51–75). Furthermore, we found that patients who suffered from autonomic dysfunctions were older [58 years (IQR 48–71)] than those who did not have autonomic dysfunctions [53 years (IQR 36–67)] ($p = 0.03$).

Thirty-five percent of patients had a mild form of GBS with a disability score < 3, and 13% of patients needed mechanical ventilation. No patients died at nadir, but nine patients (3%) died during 1-year follow-up.

CSF examination, NCS and treatment data are presented in Table 2. In the Danish GBS study population, two-thirds of the patients had CSF with the characteristic albuminocytologic dissociation, i.e., increased protein concentration with no or little increase in cell count. The most common electrophysiological subtype was AIDP, which was found in 142 of the 236 patients where NCS was available. In 78% of the patients, immunomodulating treatment was initiated, in the majority IVIg (76%).

The non-IGOS-DK cohort compared to IGOS-DK cohort

Table 1 shows an overview of key characteristics of the non-IGOS-DK group compared to the IGOS-DK group. The groups were comparable regarding age, gender and clinical variant. However, in clinical course and characteristics, some differences were identified. At nadir, IGOS patients were more severely affected than the other GBS patients as indicated by the higher GBS disability score of 4 (IQR 3–5) versus 3 (IQR 2–4). The proportion of patients with a GBS disability score ≥ 3 in the IGOS patients was 83% (95% CI 74–90) compared to 61% (55–68) in the other patients ($p = 0.0002$). IGOS-DK patients were admitted earlier after onset of weakness, reached nadir faster, and received more and earlier treatment (all $p < 0.05$). (Figs. 5, 6). There were more patients in the non-IGOS-DK group with missing NCS ($p < 0.001$) and with the AMSAN electrophysiological form of GBS ($p = 0.01$) (Table 2).

Discussion

We have conducted the first nationwide population-based study on GBS in Denmark, in which we found an IR of 1.59 per 100,000 PY (95% CI 1.42–1.78). In a prior epidemiological study of adult GBS patients from Funen, Denmark, the incidence was 1.65 per 100,000 PY [17], and several studies from Europe and North America have suggested an incidence of 1–2 per 100,000 PY with lower rates in children of 0.4 per 100,000 PY [18–21]. Using the DNPR enabled us to include all patients seen at Danish hospitals including mild cases seen as outpatients. The number of cases registered with the ICD-10 code for GBS was 522, corresponding to a positive predictive value (PPV) of 57%. After correction for the 95 cases who had debut of GBS before the study period, we would have ended up with 427 cases

Table 1 Key features of the GBS cohorts

	Danish GBS study population $n=299$	Non-IGOS-DK (ref) $n=210$	IGOS-DK $n=89$	p values
Age (years)	55 (37–67)	53 (36–67)	58 (39–66) N	NS
Sex (male)	173 (58%)	119 (57%)	54 (61%)	NS
GBS disability score at nadir (median)	3 (2–4)	3 (2–4)	4 (3–4)	$p<0.0001$
0–1	16 (6%)	16 (8%)	0	$p<0.01$
2	80 (29%)	65 (31%)	15 (17%)	$p=0.01$
3	84 (30%)	63 (30%)	21 (24%)	NS
4	81 (29%)	46 (22%)	35 (39%)	$p<0.01$
5	38 (13%)	20 (10%)	18 (20%)	$p=0.01$
Cranial nerve involvement	112 (37%)	64 (31%)	48 (54%)	$p<0.001$
Oculomotor weakness	57 (19%)	36 (17%)	21 (24%)	NS
Facial weakness	85 (28%)	46 (22%)	39 (44%)	$p=0.0002$
Bulbar weakness	62 (21%)	35 (17%)	27 (30%)	$p=0.01$
Autonomic dysfunction	47 (16%)	32 (15%)	15 (17%)	NS
Blood pressure fluctuations	19 (40%)	11 (34%)	8 (53%)	NS
Bladder dysfunction	16 (34%)	12 (38%)	4 (27%)	NS
Cardiac arrhythmias	12 (26%)	9 (28%)	3 (20%)	NS
Gastrointestinal dysmotility	5 (11%)	4 (13%)	1 (7%)	NS
Pupil dysfunction	5 (11%)	5 (16%)	0	NS
Other*	9 (19%)	4 (13%)	5 (33%)	NS
Days from onset of weakness to admission	5 (3–12)	8 (4–16)	3 (2–4)	$p<0.0001$
Days from onset of weakness to nadir	10 (6–16)	11 (7–18)	7 (4–12)	$p<0.0001$
Sensory deficits	184 (62%)	115 (55%)	69 (78%)	$p<0.001$
Pain	165 (55%)	116 (55%)	49 (55%)	NS
Clinical course				
Mortality during 1-year follow-up, number/total	9 (3%)	8 (4%)	1 (1%)	NS
Clinical subtypes				
Sensorimotor GBS	230 (77%)	167 (80%)	63 (71%)	NS
Pure motor GBS	42 (14%)	29 (14%)	13 (15%)	NS
Miller Fisher syndrome	20 (7%)	11 (5%)	9 (10%)	NS
PCB or MFS–GBS overlap syndrome	6 (2%)	3 (1%)	3 (3%)	NS
Antecedent events				
Total	210 (70%)	133 (63%)	77 (88%)	$p<0.0001$
Upper respiratory tract infection	113 (38%)	70 (33%)	43 (48%)	$p=0.02$
Gastroenteritis	66 (22%)	41 (20%)	25 (28%)	NS
Other**	34 (11%)	25 (12%)	9 (10%)	NS
Days from antecedent event to weakness onset	10 (6–17)	10 (5–19)	11 (7–15)	NS
Brighton score of diagnostic certainty				
1	155 (52%)	109 (52%)	46 (51%)	NS
2	118 (39%)	81 (39%)	37 (42%)	NS
3	6 (2%)	5 (2%)	1 (1%)	NS
4	20 (7%)	15 (7%)	5 (6%)	NS

p values indicate the difference between non-IGOS-DK and IGOS-DK

Data are number/total and (%) or median and IQR

NS non-significant, *PCB* pharyngeal-cervical-brachial variant

*Other: Abnormal sweating, temperature fluctuations, hyponatremia (SIADH), coma

**Other: Surgery, vaccination, urinary tract infection, Borrelia, Epstein–Barr viral infection, simvastatin treatment initiated, flares in asthmatic bronchitis, car accident, birth and haemolysis, intraspinal chemotherapy, colonoscopy, gallstone, muscular pain, whitlow, varicella infection, sepsis and Vogt–Koyanagi–Harada syndrome

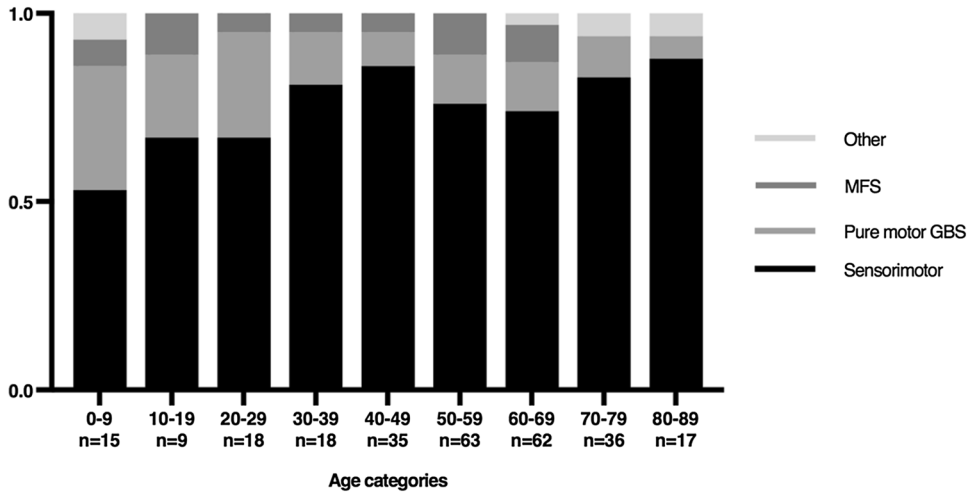

Fig. 4 Age-specific proportions of GBS clinical variants. $N = 299$. Sensorimotor $n = 231$, pure motor GBS $n = 42$, MFS $n = 20$, other $n = 6$. MFS: Miller Fisher syndrome. Other: MFS–GBS overlap syndrome, pharyngeal-cervical-brachial variant

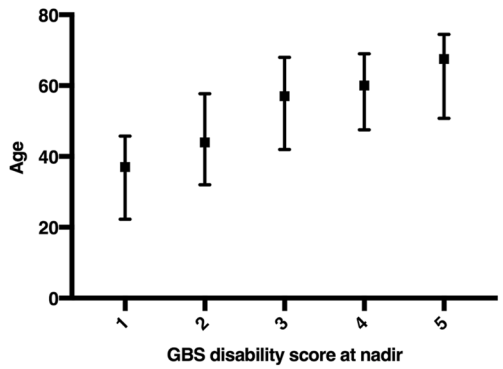

Fig. 5 Correlation between age and disability score (rs = 0.42) ($p < 0.0001$). *x*-axis shows the GBS disability score at nadir, *y*-axis shows age in years. Data are presented as median age (square) and interquartile ranges (whiskers)

(PPV = 70%) instead of the actual 299, a 43% overestimation of the incidence. This trend of overestimation of GBS cases in register-based studies without subsequent review of patient records has been described in a previous review [19]. We also reviewed records of patients coded with other inflammatory neuropathies, which identified an additional 16 patients. This is a low number considering the entire GBS population but accounted for 5 out of 20 patients with MFS (data not shown elsewhere) showing that less common variants can be missed using the disease-specific diagnostic code G61.0 for GBS.

Applying the Brighton level 1–3 diagnostic certainty on our data resulted in an incidence rate of 1.49 (95% CI 1.32; 1.67) per 100,000 PY. Although the Brighton Collaboration were developed as diagnostic criteria for vaccine safety surveillances, these highly standardized criteria are useful in comparing and describing the diagnostic certainty of GBS in epidemiological studies. In our cohort of patients who fulfilled the NINDS criteria, 52% met Brighton level 1, 91% met level 1 or 2 and 93% met level 1–3. Normal CSF and NCS were the main reasons why patients did not reach level 1 despite complete data, confirming previous studies validating the Brighton criteria [6] where patients were scored 61% in level 1, 94% in level 1–2 and 0% in level 3. In a multicenter prospective cohort study from Italy, an incidence rate of 1.84 per 100,000 PY was found in an adult population using the NINDS criteria, but only 68% of the cases met the Brighton level 1–3 criteria, mainly because of missing data [22].

In the Danish population-based cohort, we found an overall male predominance with a male to female ratio of 1.37:1 in line with previous studies [9, 20]. The male predominance seems to increase with age, a finding also described by others [20, 23, 24]. A bimodal age distribution with a small peak in the 30–39 years age group followed by a decrease from 40 to 49 years has been observed in several studies now and is also noticed in our data [11, 24–26]. Consistent with reports from other countries, there was a seasonal variation of GBS in Denmark with higher IR during the winter compared to the summer [20, 22, 23]. The proportion of the sensorimotor form increased with age, whereas the proportion of the pure motor form decreased with age. The sensorimotor form is the most common variant in all age groups corresponding to previous studies [27, 28].

The distribution in the range of clinical severities regarding the GBS disability score seems milder than described in previous series of patients. We found that 35% of patients were mildly affected and able to walk at nadir (disability score < 3) compared to 21% in the IGOS study, 27% in a large Italian cohort and only 5% in a Dutch cohort illustrating the underrepresentation of the milder affected patients in the literature [6, 11, 22].

Age is known to be a predictor of outcome in GBS [15, 29, 30] and is included in both the Erasmus GBS Outcome Score (EGOS) and the modified EGOS [31, 32] regarding

Table 2 Laboratory data and treatment of the GBS cohorts

	Danish GBS study population *n* = 299	Non-IGOS-DK	IGOS-DK	*p* values
CSF examination				
Cell count < 5/uL	229/299 (77%)	158/204 (75%)	71/89 (80%)	NS
Cell count 5–50/uL	60/299 (20%)	43/204 (20%)	17/89 (19%)	NS
Cell count > 50/uL	4/299 (1%)	3/204 (1%)	1/89 (1%)	NS
Protein concentration > 0.45 g/L	202/299 (68%)	152/206 (74%)	50/89 (56%)	$p = 0.004$
Albuminocytologic dissociation*	201/299 (67%)	149/207 (72%)	52/89 (58%)	$p = 0.03$
Days from onset of weakness to CSF examination	5 (2–11)	8 (4–14)	3 (1–5)	$p < 0.0001$
NCS before day 28 after onset				
AIDP	142/236 (60%)	86/149 (58%)	56/87 (64%)	NS
AMAN	15/236 (6%)	8/149 (5%)	7/87 (8%)	NS
AMSAN	15/236 (6%)	15/149 (10%)	0/87	$p = 0.01$
Equivocal or unresponsive nerves	45/236 (19%)	25/149 (17%)	20/87 (23%)	NS
Normal	19/236 (8%)	15/149 (10%)	4/87 (5%)	NS
NCS not available/not performed within 28 days	63/299 (21%)	61/210 (29%)	2/89 (2%)	$p < 0.001$
Initial treatment				
No treatment	65/299 (22%)	51/210 (24%)	14/89 (16%)	NS
IVIg	228/299 (76%)	153/210 (73%)	75/89 (84%)	$p = 0.03$
PE	3/299 (1%)	3/210 (1%)	0	NS
Steroids	3/299 (1%)	3/210 (1%)	0	NS
Days from onset of weakness to treatment	7 (3–13)	9 (5–16)	4 (3–6)	$p < 0.0001$

p values indicate the difference between non-IGOS-DK and IGOS-DK

Data are number/total and (%) or median and IQR

NS non-significant

*Albuminocytologic dissociation was defined as a CSF protein level > 0.45 g/L and a cell count < 50 cells/uL

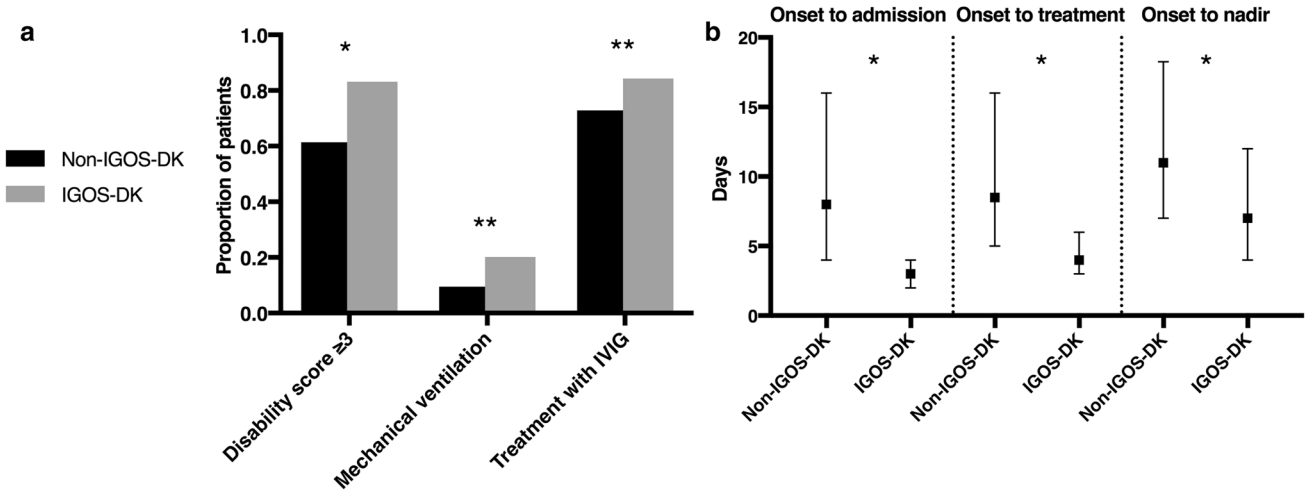

Fig. 6 **a** Differences between IGOS-DK and non-IGOS-DK cohorts. *$p < 0.0001$. **$p < 0.05$ $N = 299$. Non-IGOS-DK $n = 210$, IGOS-DK $n = 89$. *Disability score* GBS disability score, *Mechanical ventilation* ventilator dependency during follow-up. **b** Differences between IGOS-DK and non-IGOS-DK. *$p < 0.0001$. Data are presented as median with interquartile ranges

prognostic factors in GBS. However, we also found a positive correlation between disability score at nadir and age, which, to our knowledge, only has been described previously in a cohort of elderly GBS patients [33].

Previous studies have shown autonomic dysfunction in two-thirds of GBS patients [34–36]. This study has been unable to demonstrate a proportion this high with only 16% of patients with autonomic dysfunction, which in part could be explained by the high proportion of milder affected cases. The yield of routine monitoring and registration of autonomic dysfunction is debatable and there are no international guidelines on how to monitor for autonomic dysfunction [1, 34, 35, 37]. In Denmark, recording is uncommon unless it is an obvious complicating factor like cardiac arrhythmias, hyperthermia without infection, or symptomatic fluctuations in blood pressure. The most common autonomic dysfunction in our study was blood pressure fluctuations.

The results of the first 1000 patients included in IGOS internationally have recently been published [11]. This study compared patients from different geographical regions with respect to clinical variants, electrodiagnostic subtypes, treatment and clinical course (Americas/Europe, Asia without Bangladesh, and Bangladesh). Besides the lower incidence of autonomic dysfunction found throughout the Danish cohort as discussed already, the patients included in IGOS from Denmark are similar to the IGOS Americas/Europe region that includes 715 patients from 12 countries in Europe and North and South America [11].

Our data is from a prospectively enrolling register, including both hospitalized patients and less severely affected non-admitted patients, with retrospective review of all recorded cases. This enabled us to describe the full spectrum of GBS without having inclusion bias. This is emphasized by the clear differences when our population-based cohort is divided into two groups based on whether they are included in IGOS or not. The analysis showed that the hospital-based prospective study (IGOS) represents a more severely affected and more rapidly progressive subgroup of patients. At nadir, this group had a one-point higher median GBS disability score with twice as many patients in need of mechanical ventilation, had more frequent cranial nerve involvement and sensory deficits, and were more often treated with IVIg (Tables 1, 2). The low prevalence of elevated spinal fluid protein that was also found may be explained by the more rapid progression and related shorter time from onset of weakness to CSF examination in the IGOS-DK cohort [6]. Although considered to be associated with poor prognosis, the AMSAN electrophysiological subgroup of GBS was more frequent in the non-IGOS group. The majority of IGOS patients are included from larger academic centers with secondary or tertiary referral function, which is the case for most other prospective or retrospective cohort studies and case series of GBS as well. To assess whether there was referral bias toward more severely affected cases on the IGOS participating hospitals, we compared the clinical characteristics of all the patients seen at IGOS hospitals regardless of whether they were included in IGOS or not to the patients seen at non-IGOS participating hospitals in Denmark. Interestingly, we did not see any difference regarding disability score, cranial nerve involvement or time from onset to nadir, suggesting that the bias occurred by selection on the IGOS centers.

This study combines a high-quality prospective database register, the DNPR, with clinical data from retrospective review of all medical records including not only the GBS-specific diagnostic code but also codes for other inflammatory neuropathies. Clinical data was not collected by protocol which limits the amount of details and completeness of the clinical dataset; however, the diagnostic work-up of GBS is very homogeneous and only 7% could not be classified as Brighton diagnostic level 1–3 based on the availability of data. Another limitation of the study is the inhomogeneous long-term follow-up data in patient records. This aspect needs to be addressed in a prospective long-term follow-up study. We were unable to identify and review 13 out of the 1078 medical records. Twelve of the missing patients were recorded as G61.0 without having a contact to a neurological department.

In conclusion, our nationwide population-based cohort study describes the epidemiology and key clinical features of GBS in Denmark in detail. This includes a larger proportion of milder cases that do meet diagnostic criteria for GBS but are underrepresented in previous studies, as well as a previously undescribed correlation between high disability score at nadir and age. Moreover, this study is a unique control group to the IGOS study that strengthens the interpretation of the results found in IGOS. Indeed, IGOS may represent more severely affected cases with a rapid disease development and not the entire GBS population. Thus, the study highlights a need for population-based studies including the full spectrum of GBS to balance the interpretation of prospective studies.

Compliance with ethical standards

Conflicts of interest The authors received no specific funding for this work. Thomas Harbo has received speakers' honoraria from CSL Behring. Bart Jacobs reports grants from Baxalta, grants from Grifols, grants from CSL-Behring, grants from Annexon, grants from Prinses-Beatrix Spierfonds, grants from GBS-CIDP Foundation International, outside the submitted work. The remaining authors report no competing interests.

Ethical standard The manuscript does not contain patient data. Permission to obtain and process data was granted by the Danish Data Protection Agency [reference number 1-16-02-3-16] and the Danish Patient Safety Authority [reference number 3-3013-1449/1/].

References

1. van den Berg B, Walgaard C, Drenthen J et al (2014) Guillain–Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 10:469–482. https://doi.org/10.1038/nrneurol.2014.121
2. Dornonville de la Cour C, Jakobsen J (2005) Residual neuropathy in long-term population-based follow-up of Guillain–Barré syndrome. Neurology 64:246–253. https://doi.org/10.1212/01.WNL.0000149521.65474.83
3. Hughes RA, Swan AV, van Doorn PA (2014) Intravenous immunoglobulin for Guillain–Barré syndrome. In: Hughes RA (ed) Cochrane database of systematic reviews. Wiley, Chichester
4. Raphaël JC, Chevret S, Hughes RA, Annane D (2002) Plasma exchange for Guillain–Barré syndrome. In: Annane D (ed) Cochrane database of systematic reviews. Wiley, Chichester
5. Asbury AK, Cornblath DR (1990) Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 27:S21–S24. https://doi.org/10.1002/ana.410270707
6. Fokke C, van den Berg B, Drenthen J et al (2014) Diagnosis of Guillain–Barré syndrome and validation of Brighton criteria. Brain 137:33–43. https://doi.org/10.1093/brain/awt285
7. Sejvar JJ, Kohl KS, Gidudu J et al (2011) Guillain–Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599–612. https://doi.org/10.1016/j.vaccine.2010.06.003
8. Islam MB, Islam Z, Farzana KS et al (2016) Guillain–Barré syndrome in Bangladesh: validation of Brighton criteria. J Peripher Nerv Syst 21:345–351. https://doi.org/10.1111/jns.12189
9. Sejvar JJ, Baughman AL, Wise M, Morgan OW (2011) Population incidence of Guillain–Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 36:123–133. https://doi.org/10.1159/000324710
10. Jacobs BC, van den Berg B, Verboon C et al (2017) International Guillain–Barre Syndrome Outcome Study (IGOS): protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain–Barre syndrome. J Peripher Nerv Syst. https://doi.org/10.1111/jns.12209
11. Doets AY, Verboon C, van den Berg B et al (2018) Regional variation of Guillain–Barré syndrome. Brain 141:2866–2877. https://doi.org/10.1093/brain/awy232
12. Wakerley BR, Uncini A, Yuki N (2014) Guillain–Barre and Miller Fisher syndromes–new diagnostic classification. Nat Rev Neurol 10:537–544. https://doi.org/10.1038/nrneurol.2014.138
13. Wakerley BR, Yuki N (2014) Pharyngeal-cervical-brachial variant of Guillain–Barre syndrome. J Neurol Neurosurg Psychiatry 85:339–344. https://doi.org/10.1136/jnnp-2013-305397
14. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM (1978) Controlled trial prednisolone in acute polyneuropathy. Lancet 2:750–753. https://doi.org/10.1016/S0140-6736(78)92644-2
15. Hadden RDM, Cornblath DR, Hughes RAC et al (1998) Electrophysiological classification of Guillain–Barré syndrome: clinical associations and outcome. Ann Neurol 44:780–788. https://doi.org/10.1002/ana.410440512
16. Statistics Denmark (2017) Statbank Denmark. http://www.statistikbanken.dk/statbank5a/default.asp?w=1280. Accessed 16 April 2017
17. Leo CA, Sindrup SH, Gaist D (2010) Unchanged incidence of Guillain–Barre syndrome in the Funen county during a decade. Ugeskr Laeger 172:3093–3097
18. Sejvar JJ, Baughman AL, Wise M, Morgan OW (2011) Population incidence of Guillain–Barre syndrome: a systematic review and meta-analysis. Neuroepidemiology 36:123–133. https://doi.org/10.1159/000324710
19. McGrogan A, Madle GC, Seaman HE, de Vries CS (2009) The epidemiology of Guillain–Barré syndrome worldwide. A systematic literature review. Neuroepidemiology 32:150–163. https://doi.org/10.1159/000184748
20. Hense S, Schink T, Kreisel SH et al (2014) Estimation of background incidence rates of Guillain-Barré syndrome in Germany—a retrospective cohort study with electronic healthcare data. Neuroepidemiology 43:244–252. https://doi.org/10.1159/000369344
21. Govoni V, Granieri E (2001) Epidemiology of the Guillain–Barré syndrome. Curr Opin Neurol 14:605–613
22. Benedetti MD, Pugliatti M, D'Alessandro R et al (2015) A multicentric prospective incidence study of Guillain–Barré syndrome in Italy. The ITANG Study. Neuroepidemiology 45:90–99. https://doi.org/10.1159/000438752
23. Delannoy A, Rudant J, Chaignot C et al (2017) Guillain–Barré syndrome in France: a nationwide epidemiological analysis based on hospital discharge data (2008–2013). J Peripher Nerv Syst 22:51–58. https://doi.org/10.1111/jns.12202
24. Sipilä JOT, Soilu-Hänninen M, Ruuskanen JO et al (2017) Epidemiology of Guillain–Barré syndrome in Finland 2004–2014. J Peripher Nerv Syst 22:440–445. https://doi.org/10.1111/jns.12239
25. Peric S, Milosevic V, Berisavac I et al (2014) Clinical and epidemiological features of Guillain–Barre syndrome in the Western Balkans. J Peripher Nerv Syst 19:317–321. https://doi.org/10.1111/jns.12096
26. Kaplan JE, Schonberger LB, Hurwitz ES, Katona P (1983) Guillain–Barre syndrome in the United States, 1978–1981: additional observations from the national surveillance system. Neurology 33:633–637
27. Rabie M, Nevo Y (2009) Childhood acute and chronic immune-mediated polyradiculoneuropathies. Eur J Paediatr Neurol 13:209–218. https://doi.org/10.1016/j.ejpn.2008.04.009
28. Asbury AK, Asbury A, Carrell-Krusen Symposium invited lecture new concepts of Guillain–Barré syndrome
29. Witsch J, Galldiks N, Bender A et al (2013) Long-term outcome in patients with Guillain–Barré syndrome requiring mechanical ventilation. J Neurol 260:1367–1374. https://doi.org/10.1007/s00415-012-6806-x
30. Rajabally YA, Uncini A (2012) Outcome and its predictors in Guillain–Barre syndrome. J Neurol Neurosurg Psychiatry 83:711–718. https://doi.org/10.1136/jnnp-2011-301882
31. van Koningsveld R, Steyerberg EW, Hughes RAC et al (2007) A clinical prognostic scoring system for Guillain–Barré syndrome. Lancet Neurol 6:589–594. https://doi.org/10.1016/S1474-4422(07)70130-8
32. Walgaard C, Lingsma HF, Ruts L et al (2011) Early recognition of poor prognosis in Guillain–Barre syndrome. Neurology 76:968–975. https://doi.org/10.1212/WNL.0b013e3182104407
33. Peric S, Berisavac I, Stojiljkovic Tamas O et al (2016) Guillain–Barré syndrome in the elderly. J Peripher Nerv Syst 21:105–110. https://doi.org/10.1111/jns.12163
34. Flachenecker P (2007) Autonomic dysfunction in Guillain–Barré syndrome and multiple sclerosis. J Neurol 254:II96–II101. https://doi.org/10.1007/s00415-007-2024-3
35. Anandan C, Khuder SA, Koffman BM (2017) Prevalence of autonomic dysfunction in hospitalized patients with Guillain–Barré syndrome. Muscle Nerve 56:331–333. https://doi.org/10.1002/mus.25551
36. Hadden RD, Karch H, Hartung HP et al (2001) Preceding infections, immune factors, and outcome in Guillain–Barré syndrome. Neurology 56:758–765. https://doi.org/10.1212/WNL.56.6.758
37. Zaeem Z, Siddiqi ZA, Zochodne DW (2018) Autonomic involvement in Guillain-Barré syndrome: an update. Clin Auton Res. https://doi.org/10.1007/s10286-018-0542-y