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ORIGINAL COMMUNICATION

Long-term outcome in patients with Guillain–Barré syndrome requiring mechanical ventilation

J. Witsch · N. Galldiks · A. Bender · R. Kollmar · J. Bösel · C. Hobohm · A. Günther · I. Schirotzek · K. Fuchs · E. Jüttler

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Abstract We aimed to determine long-term disability and quality of life in patients with Guillain–Barré syndrome (GBS) who required mechanical ventilation (MV) in the acute phase. Our retrospective cohort study included 110 GBS patients admitted to an intensive care unit and requiring MV (01/1999–08/2010) in nine German tertiary academic medical centers. Outcome was determined 1 year or longer after hospital admission using the GBS disability scale, Barthel index (BI), EuroQuol-5D (EQ-5D) and Fatigue Severity Scale. Linear/multivariate regression analysis was used to analyze predicting factors for outcome. Mean time to follow up was 52.6 months. Hospital mortality was 5.5 % and long-term mortality 13.6 %. Overall 53.8 % had a favorable outcome (GBS disability score 0–1) and 73.7 % of survivors had no or mild disability (BI 90–100). In the five dimensions of the EQ-5D "mobility", "self-care", "usual activities", "pain" and "anxiety/depression" no impairments were stated by 50.6, 58.4, 36.4, 36.4 and 50.6 % of patients, respectively. A severe fatigue syndrome was present in 30.4 % of patients. Outcome was statistically significantly correlated with age, type of therapy and number of immunoglobulin courses. In GBS-patients requiring MV in the acute phase in-hospital, and long-term mortality are lower than that in previous studies, while long-term quality of life is compromised in a large fraction of patients, foremost by immobility and chronic pain. Efforts towards improved treatment approaches should address autonomic dysfunction to further

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J. Witsch (✉) · E. Jüttler
Center for Stroke Research Berlin (CSB),
Charité University Medicine Berlin,
Charitéplatz 1, 10117 Berlin, Germany
e-mail: Jens.Witsch@charite.de

J. Witsch
Department of Neurology, Charité University Medicine,
Berlin, Germany

N. Galldiks
Department of Neurology, University of Cologne,
Cologne, Germany

N. Galldiks
Institute of Neuroscience and Medicine,
Forschungszentrum Jülich, Juelich, Germany

A. Bender
Department of Neurology, Ludwig-Maximilians-University,
Munich, Germany

A. Bender
Department of Neurology, Therapiezentrum Burgau,
Burgau, Germany

R. Kollmar
Department of Neurology, Friedrich-Alexander-University
Erlangen, Erlangen, Germany

J. Bösel
Department of Neurology, University of Heidelberg,
Heidelberg, Germany

C. Hobohm
Department of Neurology, University of Leipzig,
Leipzig, Germany

A. Günther
Department of Neurology, University of Jena,
Jena, Germany

reduce hospital mortality while improved rehabilitation concepts might ameliorate long-term disability.

Keywords Guillain–Barré syndrome · Peripheral neuropathy · Critical care · Outcome research · Mortality · Quality of life

Introduction

In patients with Guillain–Barré syndrome (GBS) poor clinical outcome is most frequent among patients who were treated in an intensive care unit (ICU) and required mechanical ventilation (MV) during the acute phase with a reported long-term mortality rate of 20 % at 12 months or longer after hospital discharge [1, 2]. ICU-complications are most often associated with prolonged ventilation, concomitant medical conditions, or old age [3–5]. However, in comparison with other neurological ICU-patients (with, e.g., cerebral ischemia, intracerebral hemorrhage or subarachnoid haemorrhage) GBS patients are more likely to survive the acute phase [6, 7]. Thus, they may suffer later from long-term consequences which are either GBS-associated, such as chronic pain and fatigue [8, 9], or a result of the ICU-treatment itself, or both. It is unclear whether these factors result in major disability or decreased quality of life in these patients.

While many studies evaluated long-term outcome and quality of life in non-ICU GBS patients [8, 10–19], few have systematically addressed these items in GBS patients who required MV [2, 20]. The largest of these studies were carried out in a patient cohort treated in a time period when modern treatment regimens were not routinely in use yet [2, 3].

Our multi-center study investigates long-term disability and quality of life ($\geq$1 year after symptom onset) in patients with GBS admitted to an ICU and requiring MV. At the outset of the study four hypotheses were formulated: (1) higher age at admission and (2) longer duration of mechanical ventilation, are associated with worse clinical long-term outcome. (3) The type of initial therapy (IVIG or plasma exchange or immune adsorption) and (4) one versus more than one courses of IVIG are not related to clinical outcome.

I. Schirotzek
Department of Neurology, University of Giessen, Giessen, Germany

K. Fuchs
Department of Anesthesiology, University of Regensburg, Regensburg, Germany

E. Jüttler
Department of Neurology, Rehabilitation and University Hospitals Ulm, Ulm, Germany

Materials and methods

Patient selection and data collection

Enrolled subjects were unselected patients presenting to one of the nine participating study centers between January 1999 and August 2010 with the diagnosis of GBS according to the criteria by Asbury and Cornblath [21]. Cases of chronic inflammatory demyelinating polyneuropathy (CIDP) were excluded.

Clinical data were recorded at the time of presentation by neurologists and intensivists and included previous medical history, signs and symptoms at presentation, diagnostic work up, latency between start of symptoms and start of therapy, as well as type and chronology of therapeutic measures. These documentations were transferred retrospectively from the patients' charts to systematic case report forms (CRF).

Ethics committee approval and patient consent

Written informed consent was given by all subjects or their legal representatives prior to study inclusion. This study was conducted according to the guidelines of good clinical practice and the declaration of Helsinki, and with the approval of the local ethics committees of all participating study centers.

Patient follow-up

Outcome data was collected by neurologists via telephone or by post using standardized versions of the respective outcome scales. If contact to the study subjects or legally authorized representative could not be established (e.g., for missing address data) data on mortality was gathered by contacting the local registration offices.

Baseline data and outcome

Baseline data drawn from the patients' charts included: age/sex, latency between first symptoms and hospital admission, length of hospital and ICU stay, latency between symptom onset and therapy initiation, duration of mechanical ventilation, infections preceding GBS (gastrointestinal/pulmonary/other), especially Campylobacter jejuni infection and other GBS-related infections (Epstein–Barr virus, Cytomegalovirus, Mycoplasma pneumoniae, Haemophilus influenzae) or concomitant diseases (infectious/respiratory/general), vaccinations preceding GBS (both within 4 weeks before hospital admission), clinical features (bilateral facial palsy, paresis of the upper extremities, bulbar symptoms, autonomic dysregulation), detection of ganglioside antibodies, electromyographic

(EMG) pattern (demyelinating vs. mixed peripheral nerve lesion), tracheostomy, complications during the ICU-stay: tracheobronchitis, pneumonia, pneumothorax, tracheostomy-related complications, sepsis, gastrointestinal bleeding, deep venous thrombosis (DVT), syndrome of inappropriate antidiuretic hormone secretion (SIADH), acute renal failure, newly diagnosed malignancies, sequence of GBS-specific therapy (IVIG vs. plasma exchange vs. immune adsorption), number of courses of IVIG (one course of 3–6 days IVIG 2 g/kg vs. >1 course).

Outcome was assessed as described ≥12 months after symptom onset using the GBS disability scale for classification of the patient's function in the categories: 0, healthy; 1, minor symptoms or signs, able to run; 2, able to walk >5 m without assistance but unable to run; 3, able to walk >5 m with assistance; 4, bed- or chair-bound; 5, requiring assisted ventilation for at least part of the day; 6, dead [22]. Competence in daily living was assessed using a validated version of the Barthel Index (BI) [23, 24]. GBS disability scores 0–1, 2–3 and >3 were defined as mild, moderate and severe disability, respectively. Equivalently, scores on the BI of 90–100, 60–85 and <60 were defined as mild, moderate and severe disability.

Quality of life was assessed using a validated version of the EQ-5D, a five-dimensional assessment scale with the categories "mobility", "self-care" "usual activities", "pain/discomfort", and "anxiety/depression" [25–27]. Study subjects selected 1–5 graded responses for each dimension, indicating "no", "slight", "moderate", "severe" or "extreme" problems in that dimension. Here the results are expressed as a five digit code, providing a graduation between the different qualities that are assessed by the EQ-5D.

Fatigue was assessed with the Fatigue Severity Scale (FSS), a simple nine-item questionnaire which has been used before in GBS patients [8, 28, 29]. Study subjects rank their responses on a scale from 1 ("strongly disagree") to 7 ("strongly agree"). The result is expressed as the mean value of nine answers; a mean value of ≥5.5 indicates severe fatigue.

Statistical analysis

All analyses were performed using the SPSS 13.0 software package (SPSS Inc) and the "R" statistical language system (version 2.15.0). The figure was created using Matlab (The Mathworks, Natick, USA). Data were expressed as mean or median and range. Percentages were expressed as fractions of all patients included in the study. Linear multiple regression analysis was used to analyze the influence of age and duration of ventilation for the different outcome scales (GBS disability scale, BI, EQ-5D, FSS). Potential differences between clinical outcomes in a group receiving one cycle of IVIG versus a group receiving >1 cycle of IVIG were tested using Welch's t test. Potential differences of clinical outcome in different therapy groups ("IVIG", "plasma exchange", "immune adsorption") were tested using one-way analysis of variance (ANOVA). Due to the exploratory nature of this retrospective study, no correction was made for multiple testing. For patients who had died, the worst score was chosen for quality-of-life and fatigue scales. Two-tailed p values below 0.05 were considered statistically significant.

Results

A total of 110 ICU patients satisfying the study criteria were identified, two of them were children. The demographic and clinical characteristics and treatment specifications are summarized in Table 1. Six patients died in hospital (5.5 %; mean age 71.5 years, range 57–83). In 3/6 the cause of death was autonomic dysfunction and regarded as directly GBS-related. In the remaining patients causes of death included cardiac disease (2/6) and autoimmune anemia (1/6), both were regarded as not directly related to GBS. 4/6 patients died while being mechanically ventilated.

Of all patients 19 (17.3 %) were lost to long-term follow-up. General long-term condition using the GBS disability scale was available for 91 patients (82.7 %). Disability of survivors using the Barthel Index was assessed in 76 patients (79.2 % of survivors). Long-term quality of life was available for 77 (80.2 %, EQ-5D) and 69 patients (71.9 %, Fatigue Severity Scale) respectively.

Long-term mortality and disability

At follow-up 15 patients (13.6 %) had died, nine of them after hospital discharge. These patients had a mean age of 72.7 years (median 78; range 41–85). In 4/9 patients the cause of death could not be determined retrospectively. In 4/9 patients causes of death were unrelated to GBS and included intracranial hemorrhage, heart failure, newly diagnosed leukemia and a lethal complication after abdominal surgery. One patient died of pneumonia with respiratory insufficiency. An association to the previous GBS was unclear.

Among the survivors, 53.8 % had a favorable outcome (defined as GBS disability score 0–1) (Fig. 1a), 27.5 % had an intermediate (GBS disability score 2–3) and 18.7 % had an unfavorable outcome (GBS disability score >3). The latter group included the 15 deceased patients (GBS disability score 6); 73.7 % of survivors in whom the respective data were available had no or mild disability (BI score 90–100, Fig. 1b); 15.8 % were moderately disabled (BI score 60–85); and 10.5 % were severely disabled (BI score <60).

Table 1 Cohort characteristics

Number of patients, *n*	110
Age on admission, median (min max)	58 (2–85)
Gender: female (%)	40.0
Time to follow-up (months), mean (min max)	52.6 (12–149)
Total length of hospital stay (days), mean (median)	49.5 (37.5)
Length of stay in the ICU, mean, (median)	42.1 (30)
Latency between symptom onset and therapy initiation, mean (median)	3.7 (2)
Duration of mechanical ventilation mean, (median)	40.7 (28)
Clinical features	
Bilateral facial paresis, *n* (%)	50 (45.5)
Bulbar symptoms, *n* (%)	60 (54.5)
Upper extremity paresis, *n* (%)	94 (85.5)
Autonomic dysregulation, *n* (%)	50 (45.5)
Previous vaccination, *n* (%)	2 (1.8)
Detection of *Campylobacter jejuni*, *n* (%)	17 (15.5)
Electrophysiology	
Demyelinating n (%)	23 (20.9)
Mixed n (%)	70 (63.6)
Complications, *n* (%)	85 (77.3)
Tracheobronchitis, *n* (%)	14 (12.7)
Pneumonia, *n* (%)	67 (60.9)
Pneumothorax, *n* (%)	6 (5.5)
Tracheostoma-associated, *n* (%)	6 (5.5)
Sepsis, *n* (%)	11 (10.0)
GI-bleeding, *n* (%)	1 (0.9)
DVT, *n* (%)	1 (0.9)
SIADH, *n* (%)	2 (1.8)
Acute renal failure, *n* (%)	4 (3.6)
Newly diagnosed malignancies, *n* (%)	0 (0.0)
Initial therapy	
IVIG, *n* (%)	61 (55.5)
>1 cycle IVIG, *n* (%)	24 (21.8)
Plasma exchange, *n* (%)	24 (21.8)
Immune adsorption, *n* (%)	15 (13.6)
Other, *n* (%)	4 (3.6)

DVT deep venous thrombosis, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *IVIG* intravenous immunoglobulins

Long-term quality of life

Panel c of Fig. 1 shows the percentage of patients without complaints in the respective dimension of the EQ-5D (i.e. EQ-5D score 1). In the distinct dimensions "mobility", "self-care", "usual activities", "pain/discomfort" and "anxiety/depression" no problems were stated by 50.6, 58.4, 36.4, 36.4 and 50.6 % respectively.

The supplementary table shows the percentages of patients without complaints in the EQ-5D categories in different age groups of GBS patients compared to a survey in the general German population [30]. Although the number of observations among GBS patients is too limited to serve for a valid statistical analysis it may be appreciated that the rate of patients without problems is lower in GBS patients in all age groups and all categories when compared to the general population.

Figure 1c shows the mean Fatigue Severity Scale scores in our patients. Of those patients who answered the FSS-questionnaire, 30.4 % had a mean score of 5.5 or higher, equivalent to a fatigue syndrome as defined by the FSS-scale.

Outcome prediction parameters

In a multiple regression analysis with age at admission and duration of mechanical ventilation as predictors, we found a higher GBS-score (0.33 units/10 years, $p = 0.007$) and lower BI-score (−6.9/10 years, $p = 0.003$) at the time of follow-up depending on the age at admission. EQ-5D scores increased with age in the dimensions "mobility" (0.30/10 years, $p < 0.001$), "self-care" (0.32/10 years, $p < 0.001$), "usual activities" (0.26/10 years, $p = 0.004$) and "pain/discomfort" (0.29/10 years, $p < 0.001$). In contrast, higher age at admission was not significantly associated with "anxiety/depression" ($p = 0.084$) or the Fatigue Severity score ($p = 0.221$). The same multiple regression analysis revealed no associations of the duration of mechanical ventilation with clinical outcome (GBS disability score $p = 0.613$; BI $p = 0.556$, FSS $p = 0.760$).

The type of initial therapy was tested as outcome prediction factor (one-way-ANOVA, Table 2). In patients initially treated with IVIG, significantly more often a favorable outcome was found for all outcome scales tested (GBS Disability Scale, Barthel Index, all dimensions of EQ-5D).

In 42 patients in whom outcome data was available, only one course of IVIG was administered. In 18 patients, two or more courses of IVIG were administered. The analysis showed more favorable outcome in patients that received >1 course of IVIG (Table 3). This observation was statistically significant for the GBS disability scale, BI and two dimensions of the EQ-5D scale ("self-care" and "usual activities"), whereas no statistically significant treatment differences were found for the dimensions "mobility", "pain/discomfort", "anxiety/depression" or for the FSS.

Discussion

To our knowledge, this current cohort is the largest group of consecutive GBS patients after mechanical ventilation to

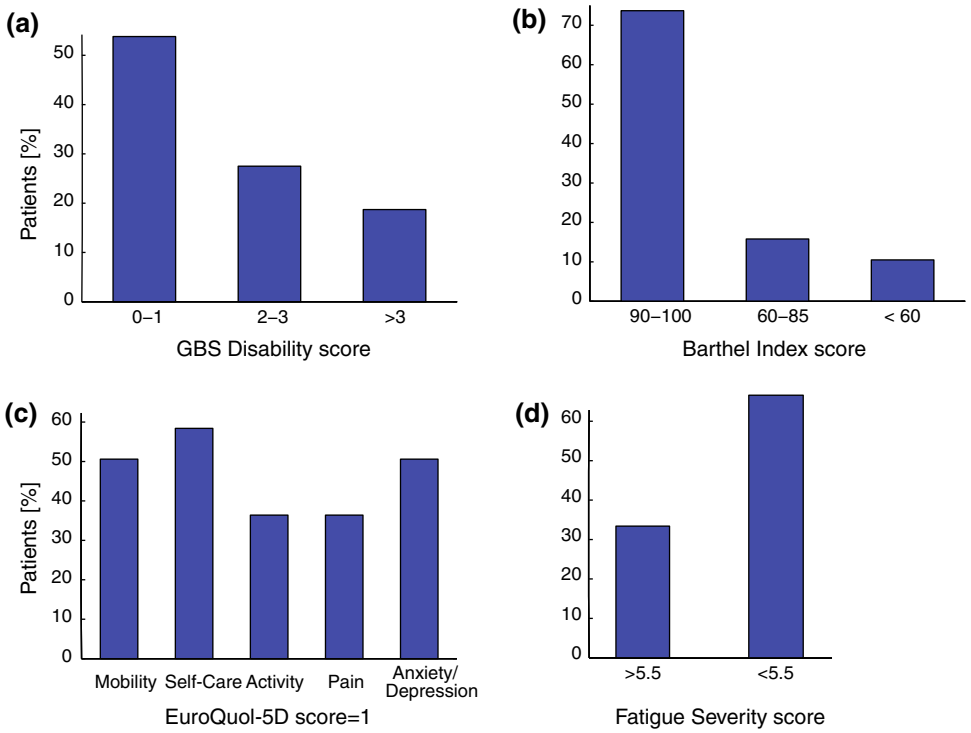

Fig. 1 Long-term disability and quality of life in patients after GBS and mechanical ventilation. **a** GBS Disability Score in $n = 91$ patients. Binning: Healthy or minor symptoms/signs (0–1), able to walk >5 m without assistance but unable to run; able to walk >5 m with assistance (2–3), bed/chair bound OR requiring assisted ventilation OR dead (>3). **b** Barthel Index Score in $n = 76$ surviving patients. Binning: mild (90–100), moderate (60–85), severe disability (<60). **c** Percentage of patients with an EQ-5D score of 1 ("no problems") in five dimensions in $n = 77$ patients. **d** Fatigue in patients with GBS and mechanical ventilation as quantified using the Fatigue Severity Scale (FSS) in $n = 69$ patients. The FSS consists of nine statements evaluating different aspects of fatigue. The patient is asked to assign a score from 1 ("completely disagree") to 7 ("completely agree") to each of these statements. A mean score of ≥5.5 is considered equivalent to severe fatigue

Table 2 Outcome for the three types of initial therapy

	IVIG ($n = 51$)	Plasma exchange ($n = 22$)	Immune adsorption ($n = 12$)	Comparison
GBS Disability Scale, mean (SD)	1.61 (1.70)	2.27 (1.86)	3.42 (2.61)	$F_{2,82} = 4.71$, $p = 0.012$
BI	83.6 (32.0)	71.4 (38.1)	41.5 (45.5)	$F_{2,82} = 7.24$, $p = 0.001$
EQ-5D mobility	2.02 (1.53)	2.82 (1.32)	3.46 (1.81)	$F_{2,83} = 6.08$, $p = 0.003$
Self-care	1.88 (1.42)	2.77 (1.54)	3.46 (1.81)	$F_{2,83} = 6.79$, $p = 0.002$
Usual activities	2.24 (1.36)	3.00 (1.35)	3.69 (1.65)	$F_{2,83} = 6.48$, $p = 0.002$
Pain/discomfort	2.08 (1.31)	2.91 (1.27)	3.38 (1.66)	$F_{2,83} = 6.23$, $p = 0.003$
Anxiety/depression	1.82 (1.26)	2.77 (1.48)	3.31 (1.70)	$F_{2,83} = 7.70$, $p < 0.001$

date in which clinical outcome and quality of life were systematically determined using validated clinical scoring systems. Of course the validity of retrospective data is limited by short-comings inherent to this study design, e.g., patient selection bias, variable treatment approaches depending on local standard operating procedures, and incomplete follow-up. Its design is not suitable for deducing definitive conclusions concerning the most beneficial treatment. Yet the present study reflects clinical outcome in a large cohort in nine university tertiary care centers. It thus may contribute to estimating the actual benefit of recent efforts that have been directed toward improving outcome in patients with severe GBS.

Previous studies have indicated that the common notion that mortality is low in GBS patients is not true for the subgroup of mechanically ventilated patients (mortality

Table 3 Outcome for the number of IVIG cycles

	One cycle IVIG ($n = 42$)	More than one IVIG cycle ($n = 18$)	Comparison
GBS Disability Scale, mean (SD)	2.26 (1.96)	1.28 (1.36)	$t_{46} = 2.23$, $p = 0.031$
FSS	4.24 (2.37)	4.81 (2.15)	$t_{38} = -0.88$, $p = 0.383$
BI	71.5 (38.8)	90.8 (23.9)	$t_{50} = -2.34$, $p = 0.023$
EQ-5D mobility	2.57 (1.56)	1.89 (1.08)	$t_{46} = 1.95$, $p = 0.057$
Self-care	2.57 (1.65)	1.56 (0.98)	$t_{52} = 2.95$, $p = 0.005$
Usual activities	2.76 (1.48)	2.00 (1.19)	$t_{40} = 2.11$, $p = 0.041$
Pain/discomfort	2.60 (1.43)	2.00 (1.19)	$t_{39} = 1.67$, $p = 0.103$
Anxiety/depression	2.33 (1.54)	1.78 (1.11)	$t_{44} = 1.56$, $p = 0.124$

BI Barthel index, *EQ-5D* EuroQuol-5D, *FSS* Fatigue Severity Scale, *IVIG* intravenous immunoglobulins

approx. 20 % after >1 year) [2]. With neuro-intensive care units and new promising treatment options having been implemented during the past decades, one would expect a beneficial effect on mortality in ventilated GBS-patients. In fact, hospital mortality in our patients (5.5 %) was markedly lower than reported in most previous studies in ventilated GBS-patients (10–20 %) [31, 32]. The reason for this is unclear. Selection bias in our cohort cannot be excluded entirely. However one other study in German GBS patients also found a mortality rate at discharge that was comparable to ours (4 %) [6]. The fact that the death of three patients in hospital (50 %) was related to autonomic dysfunction points toward the future opportunity to possibly further reduce hospital mortality by targeting GBS-related complications such as cardiac arrhythmias.

In our cohort long-term mortality was moderately lower (13.6 %) than in a cohort between 1976 and 1996 reported by Fletcher et al. [2]. However, it exceeds the expected mortality when considering the low hospital mortality in our patients, even after accounting for the comparably longer time to follow-up in the present study. The causes of long-term mortality in our patients could be determined in approximately half of patients and do not seem to be GBS-related. However, prospective outcome studies are warranted in order to establish causes of death and potential relationships to GBS more accurately.

More than half of patients in our study show no or only mild disability on the GBS Disability Scale, and more than 70 % have no or only mild disability on the BI. 75 % regained independent ambulation. This finding is comparable to a previous outcome study on ventilated GBS patients [2]. However, it is of note that outcome of survivors does not seem to have improved during the past two decades and that in our cohort the portion of severely disabled patients is still high at follow up (>10 % of patients).

Notably, only half of patients state no problems with "mobility" and "anxiety/depression", and only one-third report no problems in pursuing their "usual activities" or concerning the sensation of "pain". To our knowledge, there are no comparable data using the EQ-5D score in mechanically ventilated GBS patients. The focus of previous studies was mainly on functional outcome scales, and the comparably good results might have contributed to the notion that outcome after GBS is usually favorable, taking little notice of subjective life-quality. The EQ-5D score does not allow for identifying a potential relationship between quality-of-life impairment and a specific disease-related aspect and our findings may be due to diseases or circumstances not related to GBS. Nevertheless, we speculate that impairment of daily activities is most likely due to residual neuropathy including pain [10] which may not be pronounced enough to influence or be detected by the disability scales but may strongly influence subjective well-being.

Compared to previous findings, our results suggest that in the long-term chronic fatigue might be an overestimated problem in GBS patients, even after ICU treatment. 30 % of our patients showed severe fatigue as defined by the Fatigue Severity Scale. This finding is in contrast to previous studies. For example, one larger study of 113 GBS and CIDP patients and 113 age- and sex-matched controls reported a fatigue syndrome in 80 % of patients [8]. The mean FSS score in that study was 5.6 compared to a mean of 3.8 in our patients. The discrepancy may be explained by the more heterogeneous patient group in the previous study, which included patients with CIDP, and by the timing of fatigue assessment (partly assessed in patients that were still acutely ill). Our findings are comparable to another previous long-term follow up study in 42 GBS patients and 50 controls where a mean score of 3.8 on the FSS scale was found in GBS patients, with no significant difference between patients and controls [13].

In mechanically ventilated GBS patients, age has consistently been demonstrated to be an independent predictor of mortality and lower functional outcome [2, 4]. This was confirmed in our study. In a previous study the duration of mechanical ventilation did not significantly differ between

patients with a favorable versus unfavorable outcome [4], nor was it shown to be an independent predictor of long-term outcome in multivariate analysis [2]. This is also the case in our patient sample. In contrast, in another study including 796 neuro-ICU patients including GBS patients, duration of ventilation was found do be an independent predictor of functional outcome [6]. One may speculate that duration of ventilation in many neuro-ICU patients is associated with higher acute mortality due to respiratory complications, but also with the severity of the disease and thereby with recovery and long-term outcome. GBS-induced prolonged ventilation presumably may depend mainly on the degree of acute nerve damage and time of recovery, which in turn, however, may not be significantly associated with the degree of long-term recovery.

Different types of initial therapy in our study were associated with different functional outcomes on disability scales and EQ5-D in all dimensions, with initial IVIG-treatment yielding the best outcomes (Table 2). This finding has, however, to be interpreted with great caution, because in the present study group sizes were limited (IVIG $n = 51$, plasma exchange $n = 22$, immune adsorption $n = 12$). We also found significantly better outcomes in patients receiving more than one course of IVIG on both disability scores and in the dimensions "self-care" and "usual activities" in EQ-5D testing. This finding was quite unexpected, since to our knowledge in only one small study a beneficial effect of >1 course of IVIG was reported so far [33]. Repeated IVIG cycles are often given to patients with severe disease who are not responding after the initial IVIG administration. However, rationales for second-cycle administration are not standardized, and are given at the discretion of the treating physician. Assuming a worse degree of baseline disability in patients treated with >1 cycle of IVIG one might even expect worse clinical outcome in these patients. In our patient sample, initial upper extremity paresis—as a measure of baseline disability—was not more frequently reported in patients receiving >1 cycle of IVIG, suggesting that these patients were not more severely disabled during the initial hospital stay. However, the rational for second IVIG cycle administration, e.g., absence of clinical improvement after the first cycle, was usually not reported by the participating study centers in the present study. The unexpectedly better outcome in patients receiving >1 cycle IVIG might thus not be related to unequal patient groups but rather to variable rationales for second IVIG cycle administration in different study centers.

We believe that due to the retrospective nature of our study and possible biases, we should be very careful in interpreting our findings. Therefore we did not go into more detail concerning this finding, because it might still be a play of chance or due to selection bias. Yet, we also believe that it deserves further investigation, at least in larger multi-center studies and with a prospective approach, or better in randomized controlled trials, including more patients than were included in the present study. This would, of course, be the appropriate approach to provide valid answers to these problems.

Conclusions

(1) Acute and long-term mortality in GBS-patients who require mechanical ventilation have decreased during the past decades. (2) Long-term quality of life is compromised in a considerable number of survivors, foremost by chronic pain, reduced ability to carry out pre-morbid activities and decreased mobility. (3) Older age was a predictor for clinical outcome whereas duration of MV was not. In our sample initial IVIG treatment was superior compared to other treatment approaches and >1 course of IVIG seemed to be beneficial compared to one course only. The latter two observations merit reevaluation in future prospective studies.

On the one hand, our results reflect successful constant efforts, undertaken during the past decades, to improve treatment and intensive care for GBS patients. On the other hand, they provide potential starting points for future prospective investigations with the goal to further reduce mortality, e.g., by finding therapeutic measures to tackle autonomic dysfunction in GBS patients, and to ameliorate long-term consequences of the disease, e.g., by developing improved concepts of long-term care for the affected patients.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard This study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in 1964 Declaration of Helsinki.

References

1. Winer JB, Hughes RA, Greenwood RJ, Perkin GD, Healy MJ (1985) Prognosis in Guillain–Barré syndrome. Lancet 1:1202–1203
2. Fletcher DD, Lawn ND, Wolter TD, Wijdicks EF (2000) Long-term outcome in patients with Guillain–Barré syndrome requiring mechanical ventilation. Neurology 54:2311–2315
3. Henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wijdicks EF (2003) The morbidity of Guillain–Barré syndrome admitted to the intensive care unit. Neurology 60:17–21

4. Kohrmann M, Huttner HB, Nowe T, Schellinger PD, Schwab S (2009) Mechanical ventilation in Guillain–Barré syndrome: does age influence functional outcome? Eur Neurol 61:358–363
5. Lawn ND, Wijdicks EF (1999) Fatal Guillain–Barré syndrome. Neurology 52:635–638
6. Kiphuth IC, Schellinger PD, Kohrmann M et al (2010) Predictors for good functional outcome after neurocritical care. Crit Care 14:R136
7. Ng KK, Howard RS, Fish DR et al (1995) Management and outcome of severe Guillain–Barré syndrome. QJM 88:243–250
8. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA (1999) Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology 53:1648–1654
9. Garssen MP, Bussmann JB, Schmitz PI et al (2004) Physical training and fatigue, fitness, and quality of life in Guillain–Barré syndrome and CIDP. Neurology 63:2393–2395
10. 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
11. Chio A, Cocito D, Leone M, Giordana MT, Mora G, Mutani R (2003) Guillain–Barré syndrome: a prospective, population-based incidence and outcome survey. Neurology 60:1146–1150
12. Bernsen RA, de Jager AE, Schmitz PI, van der Meche FG (1999) Residual physical outcome and daily living 3 to 6 years after Guillain–Barré syndrome. Neurology 53:409–410
13. Rudolph T, Larsen JP, Farbu E (2008) The long-term functional status in patients with Guillain–Barré syndrome. Eur J Neurol 15:1332–1337
14. Nagashima T, Nishimoto Y, Hirata K, Yuki N (2004) Outcome after Guillain–Barré syndrome: comparison of motor function status and changes in social life. Rinsho Shinkeigaku 44:50–53
15. Vedeler CA, Wik E, Nyland H (1997) The long-term prognosis of Guillain–Barré syndrome. Evaluation of prognostic factors including plasma exchange. Acta Neurol Scand 95:298–302
16. Koeppen S, Kraywinkel K, Wessendorf TE et al (2006) Long-term outcome of Guillain–Barré syndrome. Neurocrit Care 5:235–242
17. Davidson I, Wilson C, Walton T, Brissenden S, Campbell M, McGowan L (2010) What constitutes a 'good' recovery outcome in post-acute Guillain–Barré syndrome? Results of a nationwide survey of post-acute GBS sufferers in the United Kingdom. Eur J Neurol 17:677–683
18. Bersano A, Carpo M, Allaria S, Franciotta D, Citterio A, Nobile-Orazio E (2006) Long term disability and social status change after Guillain–Barré syndrome. J Neurol 253:214–218
19. Bernsen RA, de Jager AE, Schmitz PI, van der Meche FG (2002) Long-term impact on work and private life after Guillain–Barré syndrome. J Neurol Sci 201:13–17
20. Dhar R, Stitt L, Hahn AF (2008) The morbidity and outcome of patients with Guillain–Barré syndrome admitted to the intensive care unit. J Neurol Sci 264:121–128
21. Asbury AK, Cornblath DR (1990) Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 27(Suppl):S21–S24
22. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM (1978) Controlled trial prednisolone in acute polyneuropathy. Lancet 2:750–753
23. Mahoney FI, Barthel DW (1965) Functional Evaluation: The Barthel Index. Md State Med J 14:61–65
24. Heuschmann PU, Kolominsky-Rabas PL, Nolte CH et al (2005) The reliability of the german version of the Barthel-index and the development of a postal and telephone version for the application on stroke patients. Fortschr Neurol Psychiatr 73:74–82
25. The EuroQol Group (1990) EuroQol–a new facility for the measurement of health-related quality of life. Health Policy 16:199–208
26. Wu AW, Jacobson DL, Berzon RA et al (1997) The effect of mode of administration on medical outcomes study health ratings and EuroQol scores in AIDS. Qual Life Res 6:3–10
27. Puhan MA, Ahuja A, Van Natta ML, Ackatz LE, Meinert C (2011) Interviewer versus self-administered health-related quality of life questionnaires—does it matter? Health Qual Life Outcomes 9:30
28. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46:1121–1123
29. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR (2008) Validation of the fatigue severity scale in a Swiss cohort. Sleep 31:1601–1607
30. Konig HH, Bernert S, Angermeyer MC (2005) Health Status of the German population: results of a representative survey using the EuroQol questionnaire. Gesundheitswesen 67:173–182
31. Ali MI, Fernandez-Perez ER, Pendem S, Brown DR, Wijdicks EF, Gajic O (2006) Mechanical ventilation in patients with Guillain–Barré syndrome. Respir Care 51:1403–1407
32. Netto AB, Taly AB, Kulkarni GB, Uma Maheshwara Rao GS, Rao S (2011) Prognosis of patients with Guillain–Barré syndrome requiring mechanical ventilation. Neurol India 59:707–711
33. Farcas P, Avnun L, Frisher S, Herishanu YO, Wirguin I (1997) Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain–Barré syndrome. Lancet 350:1747