

Relevance of anxiety in clinical practice of Guillain-Barré syndrome: a cohort study

Tarek Sharshar,¹ Andrea Polito,¹ Raphaël Porcher,² Takoua Merhbene,¹ Morgane Blanc,¹ Marion Antona,¹ Marie-Christine Durand,³ Diane Friedman,¹ David Orlikowski,¹ Djillali Annane,¹ Marie-Hélène Marcadet¹

To cite: Sharshar T, Polito A, Porcher R, *et al.* Relevance of anxiety in clinical practice of Guillain-Barré syndrome: a cohort study. *BMJ Open* 2012;**2**:e000893. doi:10.1136/bmjopen-2012-000893

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-000893>).

Received 22 May 2012
Accepted 9 July 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

¹Medical Intensive Care Unit, Raymond Poincaré Teaching Hospital, Garches, France

²Biostatistics and Medical Computer Science Department, Saint-Louis Teaching Hospital, Paris, France

³Functional Testing Department, Raymond Poincaré Teaching Hospital, Garches, France

Correspondence to

Pr Tarek Sharshar;
tarek.sharshar@rpc.aphp.fr

ABSTRACT

Objectives: Illness is often associated with anxiety, but few data exist about the prognostic significance of this phenomenon. To address this issue, we assessed whether patient anxiety is associated with subsequent need for intubation in Guillain-Barré syndrome (GBS).

Design: Incident case-cohort study.

Setting: Acute secondary care in a teaching hospital (France) from 2006 to 2010.

Participants: 110 adult GBS patients. Either language barrier or cognitive decline that precluded understanding was considered as exclusion criteria.

Primary outcome: Acute respiratory failure.

Interventions: At admission, anxiety and clinical factors (including known predictors of respiratory failure: delay between GBS onset and admission, inability to lift head, vital capacity (VC)) were assessed and related to subsequent need for mechanical ventilation (MV). Anxiety was assessed using a Visual Analogical Scale (VAS), the State Anxiety Inventory form Y1 (STAI-Y1) score and a novel-specific questionnaire, evaluating fears potentially triggered by GBS. Patients were asked to choose which they found most stressful from weakness, pain, breathlessness and uncertainty.

Results: 23 (22%) were subsequently ventilated. Mean STAI-Y1 was 47.2 (range 22–77) and anxiety VAS 5.2 (range 0–10). STAI was above 60/80 in 22 (21%) patients and anxiety VAS above 7/10 in 28 (27%) patients. Fear of remaining paralysed, uncertainty as to how the disease would progress and fear of intubation were the most stressful. Factors significantly associated with anxiety were weakness and bulbar dysfunction. STAI-Y1 was higher and uncertainty more frequent in subsequently ventilated patients, who had shorter onset-admission delay and greater weakness but not a lower VC. Uncertainty was independently associated with subsequent MV.

Conclusions: Early management of patients with GBS should evaluate anxiety and assess its causes both to adjust psychological support and to anticipate subsequent deterioration.

INTRODUCTION

Anxiety is a natural response and a necessary warning adaptation in humans. It is an unpleasant emotion triggered by anticipation

ARTICLE SUMMARY

Article focus

- Anxiety is often associated with illness but its prognosis significance remain unknown.
- We have assessed whether anxiety is predictive of subsequent respiratory failure in patients with Guillain Barré Syndrome (GBS).
- Fear of remaining paralyzed, uncertainty as to how the disease would progress and fear of intubation were most stressful.
- Anxiety was associated with weakness and bulbar dysfunction.
- Uncertainty was independently associated with subsequent respiratory failure.

Key messages

- Anxiety should be early assessed in GBS to adjust psychological support and anticipate subsequent respiratory deterioration.

Strengths and limitations of this study

- This is the first study having prospectively assessed the predictive value of anxiety, which is very often considered a subjective and non reliable symptom.
- Assessments of GBS diagnosis and course, anxiety and endpoints were done with help of validated scores and detailed questionnaires.
- The influence of patients' information by the physician has not been assessed in this single center study.

of future events, memories of past events or ruminations about the self.¹ Any acute disease can be a cause of anxiety. Anxiety is a difficult symptom for physicians to deal with as it is often considered too subjective to orientate either the diagnosis or the therapeutic approach, though physicians have been taught that it can be a warning physiological sign of a process either uncontrolled or undiagnosed, such a severe sepsis, a bleeding or a respiratory disease. To our knowledge, whether acute anxiety, its intensity or type, is predictive of subsequent deterioration has

never been addressed. We reasoned that patients with Guillain-Barré syndrome (GBS) would enable us to address this issue, as they experience a very anxiogenic disease² characterised by a progressive paralysis that often involves respiratory muscles and oropharyngeal system up to respiratory failure, the most serious short-term complication of GBS. Invasive mechanical ventilation (MV) is required in about 20% of GBS patients.^{3–9} Anticipating respiratory failure is crucial as it has been shown that delaying intubation increases the risk of aspiration, which is the main cause of death in GBS patient.^{10 11} Early clinical, biological and neurophysiological predictors of need for intubation have been identified, including a delay between GBS onset and admission less than 7 days,^{7 9} inability to lift the head,⁷ bulbar dysfunction,⁵ vital capacity (VC) less than 60% of predictive value,⁷ plasma cortisol level⁸ and bilateral conduction block in the common peroneal nerve.⁴ Therefore, the predictive value of anxiety for the occurrence of respiratory failure can be tested alongside objective predictors.

We carried out a prospective single-centre observational study to assess intensity and features of anxiety at admission and whether anxiety was predictive of subsequent respiratory failure in patients with GBS.

METHODS

Patients

Data were collected prospectively for all adult patients referred to the intensive care unit (ICU) of the Raymond Poincaré Teaching Hospital (Garches, France) who fulfilled standard diagnostic criteria for GBS¹² and were not mechanically ventilated before or within 24 h of inclusion (anxiety assessment). Exclusion criteria were non-idiopathic GBS, Miller-Fisher syndrome and either language barrier or cognitive decline that precluded understanding of anxiety questionnaires. Our ethics committee approved the study but waived the need for informed consent as the intervention was observational and the consent process was likely to influence the data collected.

Baseline parameters

Assessment of anxiety and dyspnoea

Within 24 h of admission, anxiety was assessed with State Trait Anxiety Inventory-Y1 (STAI-Y1) which is a validated score containing 20 questions, scored from 20 to 80, with a higher score indicating greater anxiety.¹³ Patients were asked a questionnaire that we developed specifically to address likely concerns specific to GBS. It contained 14 questions scored from 0 to 3 (0: not at all, 1: somewhat; 2: moderately so and 3: very much so). Following discussion within the study group, choice of its items was based on clinical experience of the areas about which GBS patients express concern, weakness, pain, breathing and uncertainties about disease progression and recovery. Patients were also asked to declare which sensation out of breathlessness, pain, weakness and uncertainty they found the

most frightening. Finally, patients also recorded their anxiety and dyspnoea level using a visual analogical scale (VAS, ranging from 0 to 10). Assessment of anxiety was always performed after the patient had been informed by the physician in charge of their care about the possible course of GBS—notably potential requirement of MV, and the potential for pain and a slow motor recovery—as well as possible treatments. All physicians had clinical experience with GBS patients and specific training on its pathophysiology, clinical course and treatment. Information from the physician could have had the effect of increasing or decreasing anxiety. Although communications could not be completely standardised, the clinical team were trained to make it clear that GBS could progress to an uncertain degree including the possibility of paralysis and need for MV, despite plasma exchanges or infusion of high-dose of intravenous immunoglobulin (IvIg).

For all these tests, the investigator assisted in completion of the scores, as although the STAI-Y1 is a self-completion questionnaire, we were concerned that motor and sensory deficit, especially in most severe patients, could hamper writing.¹³ All evaluators were trained to perform the tests by our psychologists (M-H M, M B). Patients were asked to answer quickly and evaluators asked not to comment any question of the tests. Inclusion was defined as the date of the anxiety assessment. Evaluation of anxiety took about 15 min and was done after neurological examination and VC measurement. We considered severe anxiety when STAI-Y1 was above 60¹⁴ or VAS-anxiety above 7.

Clinical and laboratory variables

The following data were recorded: (1) pre-GBS events such as diarrhoea; (2) time from motor symptom onset to admission; (3) severity of muscle weakness assessed using the disability grade and arm grade¹⁵ (table 1); (4) presence of sensory loss; (5) inability to lift the head, bulbar dysfunction and facial palsy; (6) cerebrospinal fluid (CSF) parameters and (7) liver function tests. It was also noticed that the patient was sent from an emergency room, a neurology department or another unit. Slow inspiratory VC was measured in triplicate using a spirometer (Morgan Medical; Rainham, United Kingdom), with the patient seated with the back reclined at 30°–60°, wearing a noseclip and breathing through a flange-type mouthpiece. Serum obtained at admission was studied for the presence of antibodies to *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus and Epstein-Barr virus as well as for antibodies to the gangliosides GM1, GM2, GD1a, GD1b and GQ1b. Electrophysiological testing was performed using a NEUROPACK SIGMA EMG device (M.E.S.A. Nihon Kohden) and as soon as possible, according to availability of our neurophysiologist (M-C. D.) Electrophysiological data were classified according to Hadden *et al*¹⁶ as primary demyelinating, primary axonal, unexcitable, equivocal or normal. Proximal/distal compound muscle

Table 1 Clinical and laboratory features at inclusion

Variable n (%) or median (IQR)	All patients 110	Non-ventilated 85 (77%)	Ventilated 25 (23%)
Age (years)	49.6 (16.7)	49.7 (17.1)	49.1 (15.7)
Women (%)	42 (38)	33 (39)	9 (36)
Diarrhea (%)	21 (19)	17 (20)	4 (16)
GBS onset to admission (days)	5 (3–9)	6 (4–9)	4 (2–6)
Origin department (%)			
Emergency	74 (67)	55 (65)	19 (76)
Neurology	24 (22)	19 (22)	5 (20)
Other	12 (11)	11 (13)	1 (4)
Admission to inclusion* (h)	2 (1–2)	2 (1–2)	2 (1–2)
Disability grade† > 3 (%)	42 (38)	25 (29)	17 (68)
Arm grade‡ > 2 (%)	52 (47)	31 (36)	21 (84)
Bulbar dysfunction (%)	31 (28)	24 (28)	7 (28)
Inability to lift head (%)	65 (59)	52 (61)	13 (52)
Pure motor (%)	24 (22)	18 (21)	6 (24)
VC (% of predicted value)	71.4 (23.1)	71.6 (23.2)	70.7 (23.2)
Respiratory rate (cpm)	16 (14–20)	16 (14–20)	17 (15–20)
Saturation of peripheral oxygen (%)	98 (95–98)	97 (95–98)	98 (96–98)
CSF protein (g/l)	0.7 (0.5–1.14)	0.72 (0.52–1.14)	0.62 (0.47–0.99)
No antiganglioside Ab (%)	54 (49)	41 (48)	13 (52)
Liver dysfunction (%)	15 (14)	10 (12)	5 (20)
Demyelinating electrophysiology (%)§	25 (57)	19 (53)	6 (75)
Baseline plasma cortisol level (ng/ml)	181 (132–252)	180 (139–250)	181 (105–236)
Plasma exchange (%)	57 (32)	51 (60)	6 (24)
Ivlg (%)	53 (48)	31 (36)	22 (88)
Time from inclusion to MV (days)			3 (2–4)

Decision for MV was based on presence of one major criterion or two minor criteria. Major criteria: (1) intolerable respiratory distress, (2) $\text{PaCO}_2 > 6.4$ kPa, (3) $\text{PaO}_2 < 7.5$ kPa breathing room air and (4) VC of 15 ml/kg or less. Minor criteria: (1) inefficient cough reflex, (2) inability to clear bronchial secretions despite vigorous chest physiotherapy, (3) severe bulbar dysfunction defined as repeated coughing and aspiration after swallowing and (4) atelectasis on a chest radiograph.^{17–19}

*Inclusion is the time of anxiety assessment; in all patients who required MV, the time from inclusion to EMV was longer than 24 h.

†Disability grade: 0, healthy, no signs or symptoms; 1, minor symptoms or signs and able to run; 2, able to walk 5 m across an open space without assistance; 3, able to walk 5 m across an open space with the help of one person and a waist-level walking-frame; 4, chairbound/bedbound: unable to walk as in 3; 5, requires assisted ventilation and 6, dead.¹⁵

‡Arm grade: 0, normal; 1, minor symptoms or signs but able to put hand on top of head when sitting with head upright and able to oppose the thumb to each fingertip; 2, able to do either of the tasks in 1 but not both; 3, some movements but unable to perform either of the tasks in 2; 4, no movement and 5, dead.¹⁵

§Available in 66 (60%) patients.

Ab, antibodies; CJ, *Campylobacter jejuni*; CMV, cytomegalovirus; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; Ivlg, intravenous immunoglobulin; MV, mechanical ventilation; N, number; VC, vital capacity.

action potential (p/d CMAP) ratio of the common peroneal nerve was assessed as it has been identified as a predictor of respiratory failure.⁴ Results of liver function test and blood sodium levels were collected as well as plasma cortisol levels.

Neurological examination (included interview of the patient) and measurement of VC were first done, taking less than 30 min. Biological tests were done at the time of admission. Lumbar puncture was not done once again if CSF analysis was performed prior to admission in our department. Otherwise, it was usually done within the 12 h after admission.

Follow-up

Criteria for MV

The decision to use MV was left at the discretion of the physician in charge of the patient. However, MV was used routinely in patients who met at least one major criterion

or two minor criteria, as follows: major criteria, (1) intolerable respiratory distress, (2) $\text{PaCO}_2 > 6.4$ kPa, (3) $\text{PaO}_2 < 7.5$ kPa breathing room air and (4) VC of 15 ml/kg or less; minor criteria, (1) inefficient cough, (2) inability to clear bronchial secretions despite vigorous chest physiotherapy, (3) severe bulbar dysfunction defined as repeated coughing and aspiration after swallowing and (4) atelectasis on a chest radiograph.^{17–19} MV was always invasive.

The physicians who decided to start MV were unaware of the results of anxiety tests (including VAS dyspnoea). In all patients who required MV, the time from inclusion to MV was longer than 12 h. Disability grade, arm grade and VC were assessed every other day during the first 8 days, then on every third day until day 29. All treatments (eg, plasma exchange or Ivlg) were recorded and were left at physician's discretion. Disability grade was also assessed at 6 months.

Statistical analyses

Qualitative variables are presented as number (%) and continuous variables as mean (SD) or median (IQR) when their distribution was skewed. Association of baseline patient characteristics and MV was tested using Fisher's exact, Student or Wilcoxon rank sum tests. Differences between groups were presented as mean differences and its 95% CI, whatever the variable distribution.

Association of baseline variables and measures of anxiety was assessed using Spearman's or Somers' Dxy rank correlation coefficients.

Risk factors for later respiratory failure were taken into account, including delay from GBS onset to admission, bulbar dysfunction, inability to raise head, VC and baseline plasma cortisol level.⁵⁻⁹ Proximal/distal CMAP ratio of the common peroneal nerve was not incorporated as electrophysiological testing was not performed at the same time of anxiety tests and often after intubation in patients who required MV.⁴ The adjusted analyses were carried out using multiple logistic regression models. Given the limited number of events, we chose not to conform to the 'rule of thumb' of 10 events per variable. Nonetheless, we did not enter more than one variable per five events in the models, as this showed to maintain comparable reliability as models with 10-16 events per variable.^{20 21} We thus selected a set of factors associated with subsequent MV using a stepwise model selection procedure among potential predictors. Each variable measuring anxiety was then added to this set of predictors in separate analyses.

All tests were two-sided, at a 0.05 significance level. Analyses were performed using the *R* statistical software V.2.10.1.²²

RESULTS

From December 2006 to December 2010, among the 199 patients who were referred to our department with a suspicion of GBS, 162 fulfilled GBS diagnostic criteria (Figure 1 in Supplementary data). Of these, 55 patients were not included as they were mechanically ventilated before admission (n=14), as they could not understand the anxiety tests (n=7), or because the tests could not be performed for logistical reasons (n=31) (see flow chart in supplementary file). Therefore, 110 patients were included. Seventy-four (67%) patients were having been sent from emergency room and 24 (22%) from neurology department. Patient characteristics are reported in table 1.

Description of anxiety and associated factors

In the whole group mean STAI and anxiety VAS were 47.4 (range 22-77) and 5.2 (range 0-10), respectively. STAI was above 60/80 in 23 (21%) patients and anxiety VAS above 7/10 in 28 (26%) patients. Scores for each GBS-specific question are depicted in table 2. Fear of remaining paralysed, waiting how the disease will

progress and fear of intubation were the most stressful. There was a correlation between VAS anxiety and STAI-Y1 (Spearman's rho 0.67, $p<0.0001$) and GBS-specific questionnaire (Spearman's rho 0.58, $p<0.0001$) as well as between these two scores (Spearman's rho 0.63, $p<0.0001$). Factors significantly associated with anxiety, evaluated with STAI-Y1 or GBS specific questionnaire, are depicted in table 3. Arm grade and presence of bulbar dysfunction correlated with STAI-Y1 and GBS-specific questionnaire score. Female gender and disability grade correlated with STAI-Y1. There was no statistical correlation between heart rate, respiratory rate, blood pressure, plasma cortisol levels and any scores of anxiety. There was no correlation between GBS onset to admission and any scores of anxiety, notably feeling of uncertainty ($r=0.03$ (-0.23 to 0.29), $p=0.84$). Scores of anxiety did not statistically differ between patients admitted from emergency room, neurology department or other departments. Mean value of anxiety tests did not statistically differ between psychologists (MHM and MB) and by non-psychologists evaluators (table 3).

Relationships between anxiety and subsequent MV

Twenty-five (23%) patients required MV, at a median time of 3 days after inclusion (range 1-14 days). At inclusion, patients who subsequently required MV had greater limb weakness (manifesting as worse disability and arm grades, $p=0.001$ and 0.0003 , respectively), a shorter delay from GBS onset to admission ($p=0.007$). They were also less likely to have received plasma exchange ($p<0.0001$). MV was not associated with respiratory muscle weakness (VC) nor with lower baseline plasma cortisol levels, and rates of bulbar and liver dysfunction were similar to patients who did not require ventilation (table 1).

STAI-Y1 scores were significantly higher in patients who subsequently required MV (mean difference 6.8, 95% CI 0.8 to 12.8, $p=0.028$, table 2). A higher GBS-specific score of anxiety was also found on average for these patients (mean difference 4.8, 95% CI 1.5 to 8.1, $p=0.005$). A feeling that symptoms and weakness were progressing and a feeling of breathlessness and suffocation were greater in subsequently ventilated patients as was the dyspnoea VAS (mean difference 1.2, 95% CI 0.2 to 2.3, $p=0.015$). No clear difference was found for anxiety VAS between both groups (mean difference 0.6, 95% CI -0.7 to 1.8, $p=0.44$). The two groups differed as to what they considered most stressful ($p=0.011$; table 2), with patients who subsequently underwent MV considering uncertainty to be most stressful ($p=0.025$), whereas patients who did not require MV more often cited pain or weakness. Arm grade ≥ 2 , delay between onset and admission and feeling of uncertainty were independently associated with subsequent MV (table 4). Origin department (emergency, neurology or other) did not statistically differ between patients with and without subsequent need for MV (table 1).

Table 2 Features of anxiety

Variable	All patients	Non-ventilated	Ventilated
n (%) or mean±SD or median (IQR)	110	85	25
Pre-existing psychological disorders (%)	7 (6)	5 (5)	2 (8)
Antipsychotic drugs (%)	9 (8)	6 (7)	3 (12)
Chronic alcoholism (%)	9 (8)	5 (6)	3 (12)
STAI-Y1 ¹³ (from 20 to 80)	47.4 (13.9)	45.9 (13.9)	52.7 (12.9)
GBS specific questionnaire (from 0 to 3)			
I have the feeling that my symptoms are progressing	1.9	1.6	2.5
I have the feeling that my weakness is progressing	1.8	1.6	2.5
My pain is greater since admission	0.9	1.0	0.8
I fear remaining paralysed	2.0	1.9	2.3
Waiting for confirmation of GBS diagnosis	1.8	1.8	2.1
Waiting to find out how GBS will progress	2.4	2.3	2.6
Fear of intubation	2.1	2.0	2.3
Fear of dying	1.3	1.4	1.1
Admission to ICU is stressful	1.0	1.0	0.9
I am worried by all the devices around me	0.8	0.7	1.0
I feel breathless	0.8	0.6	1.5
I feel that I am suffocating	0.5	0.4	0.9
I feel like I have a weight on my chest	0.8	0.8	1.0
I have pain when I breathe	0.3	0.3	0.4
Total	18.2 (8.4)	17.1 (8.5)	21.9 (6.8)
The most stressful sensation			
Pain (%)	30 (28)	26 (31)	4 (17)
Weakness (%)	51 (47)	43 (51)	8 (33)
Uncertainty (%)	25 (23)	15 (18)	10 (42)
Breathlessness (%)	3 (3)	1 (1)	2 (8)
Anxiety-VAS (from 0 to 10)	5 (3–8)	5 (3–7)	5 (4–8)
Dyspnoea-VAS (from 0 to 10)	2 (0–4)	1 (0–4)	4 (0–5)

GBS, Guillain-Barré syndrome; ICU, intensive care unit; STAI-Y1, State Trait Anxiety Inventory-Y1; VAS, visual analogical scale.

DISCUSSION

The present study showed that more than a third of GBS patients have intense anxiety at the time of their admission to ICU and that a feeling of uncertainty as to outcome was independently associated with subsequent

requirement of MV. The main determinants of anxiety were intensity of weakness and the presence of bulbar dysfunction and patients' main concerns were of remaining paralysed, being intubated and not knowing how their condition would progress.

Table 3 Association of baseline variables with anxiety

Variable	STAI-Y1 ¹³			GBS questionnaire total score		
	Correlation	95% CI	p	Correlation	95% CI	p
Age (years)	−0.06	−0.25 to 0.13	0.51	−0.10	−0.28 to 0.09	0.32
Male gender	−0.38	−0.59 to −0.17	0.0004	−0.23	−0.44 to −0.01	0.040
GBS onset to admission	−0.09	−0.28 to 0.10	0.34	−0.002	−0.19 to 0.18	0.98
Disability grade*	0.22	0.03 to 0.39	0.022	0.16	−0.03 to 0.34	0.095
Arm grade†	0.20	0.01 to 0.37	0.036	0.23	0.05 to 0.40	0.015
Bulbar dysfunction	0.29	0.06 to 0.52	0.012	0.26	0.04 to 0.49	0.022
Inability to lift head	−0.17	−0.17 to 0.21	0.85	−0.09	−0.31 to 0.12	0.39
Vital capacity‡	0.02	−0.17 to 0.21	0.85	0.01	−0.18 to 0.20	0.89

Results are Spearman or Somers' Dxy rank correlation coefficients for quantitative and binary variables, respectively.

*Disability grade: 0, healthy, no signs or symptoms; 1, minor symptoms or signs and able to run; 2, able to walk 5 m across an open space without assistance; 3, able to walk 5 m across an open space with the help of one person and a waist-level walking-frame; 4, chairbound/bedbound: unable to walk as in 3; 5, requires assisted ventilation and 6, dead.¹⁵

†Arm grade: 0, normal; 1, minor symptoms or signs but able to put hand on top of head when sitting with head upright and able to oppose the thumb to each fingertip; 2, able to do either of the tasks in 1 but not both; 3, some movements but unable to perform either of the tasks in 2; 4, no movement and 5, dead.¹⁵

‡Expressed as % of predicted value.

GBS, Guillain-Barré syndrome; VA, visual analogical scale.

Table 4 Association of anxiety features with subsequent mechanical ventilation in adjusted logistic regression models

Variable	OR (95% CI)				
	STAI-Y1 ¹³	GBS questionnaire	Anxiety-VAS	Dyspnoea-VAS	Most stressful
Arm grade* >2	7.56 (2.28 to 25.1)	6.72 (2.02 to 22.4)	8.05 (2.44 to 26.6)	7.73 (2.32 to 25.8)	7.53 (2.21 to 25.6)
GBS onset to admission (as log)	0.33 (0.14 to 0.79)	0.40 (0.18 to 0.89)	0.44 (0.20 to 0.98)	0.47 (0.21 to 1.05)	0.39 (0.16 to 0.92)
STAI-Y1	2.82 (0.85 to 9.39)				
GBS questionnaire total score	5.15 (1.06 to 24.9)				
Anxiety-VAS score	1.08 (0.44 to 2.64)				
Dyspnoea-VAS score	1.28 (0.46 to 3.57)				
Uncertainty as most frightening	4.05 (1.26 to 13.0)				

*Arm grade: 0, normal; 1, minor symptoms or signs but able to put hand on top of head when sitting with head upright and able to oppose the thumb to each fingertip; 2, able to do either of the tasks in 1 but not both; 3, some movements but unable to perform either of the tasks in 2; 4, no movement and 5, dead.¹⁵

GBS, Guillain-Barré syndrome; STAI-Y1, State Trait Anxiety Inventory-Y1; VAS, visual analogical scale.

It is interesting to note that it was not the intensity of anxiety, evaluated with various scores (ie, STAI-Y1, GBS specific score, VAS), but its object, that is uncertainty, that was most strongly associated with respiratory failure. This finding raises two issues. First, if the object of anxiety matters more than its intensity, causes of anxiety are numerous and may not have been exhaustively addressed in the present study. Thus, it is conceivable that an item other than uncertainty could have a greater predictive value. It would be useful for future work to perform more in-depth qualitative work to identify whether there are other important items that need to be considered. Certainly these data suggest that studies investigating the causes and consequences of anxiety should not be limited to a quantitative assessment of anxiety but need to evaluate it qualitatively in a way that may vary with the type of disease. The second issue is why uncertainty was so prominent. Uncertainty is inherently generated by any process that is still progressing up to a point that cannot be accurately determined. Thus, it is not surprising that GBS provokes uncertainty as it integrates these two dimensions. Indeed, the patient feels (even prior to physician) that GBS is progressing and respiratory failure cannot be predicted with 100% of accuracy, especially at an early stage.

We did not know how the patients were informed previously to their admission in our department. It is plausible that this may have worsened or reduced intensity of anxiety, but we did not know to what extent. The indirect arguments against such an influence are that the different origins differ neither for intensity of anxiety nor for incidence of respiratory failure. Moreover, anxiety may have been influenced by information provided by the physician in charge, whose view as to the likely prognosis might have been influenced by knowledge of the presence or absence of risk factors for a poor outcome. There are some arguments against this hypothesis. VC, one of the most powerful predictors, was not significantly different between

patients who did or did not subsequently require MV.^{3-9 23} Moreover, additional risk factors such as inability to lift the head, facial palsy and bulbar dysfunction were not more frequently present in patients who subsequently were mechanically ventilated.^{3-9 23} This suggests that patients were at a relatively early stage of GBS course at a point where the physician could not reliably predict outcome and thus may systematically cause an increase in anxiety in those patients who went on to be intubated. This is supported by the fact that the delay between GBS onset and admission was shorter in the current study than in previous ones carried out in our department.^{3 4 7 8} Despite these arguments, we acknowledge that we are not able to determine in what extent medical information might have influenced patient responses. Assessment of how anxiety before and after medical information was given might have been interesting but would have been hard to implement in routine clinical practice and of limited use. Indeed, most patients have already received some information about GBS before being admitted to ICU, therefore they were not naive.

Regarding the assessment of acute anxiety, we used both the validated score STAI-Y1 and developed a novel tool, the GBS-specific anxiety score. We acknowledge that the STAI-Y1 is a self-evaluation score but because motor and sensory deficit can hamper writing, we opted for administration by an investigator. STAI-Y1 has been used in various clinical situations, notably in preoperative and cardiac patients,²⁴⁻²⁷ but we thought that it might not test-specific anxieties related to GBS and admission into ICU. The items for the GBS-specific score were selected by the present investigators on the basis of their clinical experience and address major features of GBS (such as pain, weakness and breathing) and patient's concerns about disease progression and recovery and ICU environment. In this first use of the specific score we found that it correlated with STAI-Y1 and supporting its validity. This questionnaire has

disclosed that GBS patients are especially anxious about remaining paralysed, about needing to be intubated and about not knowing how the disease will progress, indicating areas which psychological support should be focused on. Finally, the intensity of anxiety has been measured with a VAS, a method that has rarely been used for this purpose. We have recently shown that anxiety and dyspnoea, both measured with help of VAS, were correlated in mechanical ventilated ICU patients,²⁸ suggesting that a VAS is an appropriate measure for the intensity of anxiety. The entire clinical examination took less than 45 min. We acknowledge that this could be tiring for the patients but the duration and 'density' of clinical examination is not unusual. We are not able to determine in what extend neurological examination could have altered the subsequent evaluation of anxiety. Addressing this issue would have required to assess whether anxiety evaluation is influenced by the order. Randomising the order of clinical, respiratory and psychological examination might be relevant theoretically. However, the fact that psychological evaluation was done after physical examination and VC measurement is absolutely consistent with the routine management.

The choice of criteria for MV was a crucial step in the design of the study. It has to be noted that our monitoring of GBS patients is currently based both on clinical examination, in particular of chest wall movement and ability to clear secretion and on VC measurement. Furthermore, to ensure that the decision to start MV would be based on objective factors, the responsible physician used internationally validated criteria,^{17–19} which we have already applied in previous studies on respiratory failure in GBS.^{3 4 7 8} In all cases, intubation was decided upon these criteria. It is unlikely that physicians in charge have under or overestimated the necessity of MV according to the intensity and type of anxiety.

As aforementioned, predictors previously identified, such as VC, bulbar dysfunction or baseline plasma cortisol level,^{3–9} were not retained in our univariate or multivariate analysis. Our main explanation is that patients have been seen at an earlier stage than in previous studies.^{3 4 7 8} This indicates that predictors of MV vary according to the stage of GBS course, and importantly that subjective symptoms (ie, anxiety, uncertainty and breathlessness) may precede objective signs (ie, weakness, decreased VC, cortisol, etc), as depicted in figure 1 and figure 2 of supplementary data.

Few studies have addressed psychological disorders in GBS. In a prospective study of 49 GBS patients, Weiss *et al*² observed that over the stay in neuro-ICU anxiety was observed in up to 82% of cases, depressive episodes in 67% and brief reactive psychosis in 25%. Motor deprivation and loss of communication were the most important causes of anxiety. Khan *et al*²⁹ reported that depression, anxiety and stress are observed in about 20% of GBS patients a median 6 years after their discharge from neuro-ICU. Therefore, these two studies have assessed anxiety during the stay and after discharge from

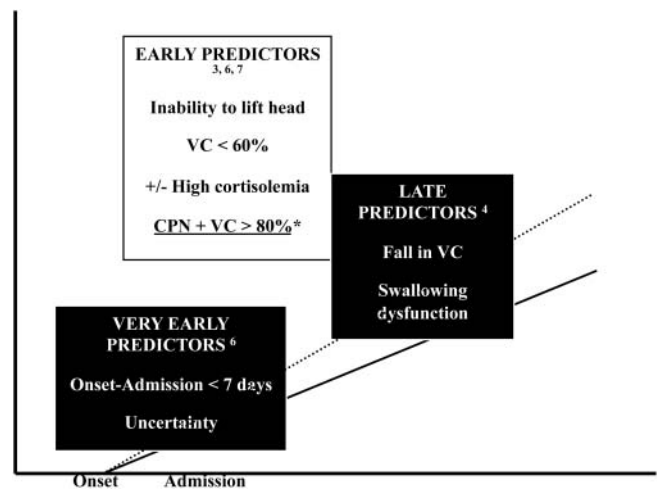


Figure 1 Predictors of invasive mechanical ventilation according to the delay from GBS onset reported in the literature. *Absent of conduction block on peroneal nerve (CPN) when associated with VC above 80% of predicted value is predictive of no occurrence of respiratory failure. CPN, conduction block on peroneal nerve; MV, mechanical ventilation; VC, vital capacity; onset-admission <7 days: delay from onset to admission <7 days.

the ICU, respectively, whereas the present study has focused on anxiety at admission. Altogether, these studies are complementary; indicating that psychological support is required at all stages of GBS course and identifying at different stages the causes of anxiety and its risk factors. Thus, psychological support should focus on issues around 'intubation' and 'uncertainty' and 'recovery' at admission and communication during stay in neuro-ICU. An additional finding of the present study is that swallowing dysfunction is an important cause of anxiety. Although perhaps unsurprising as it is clearly a threat of aspiration and airway obstruction, the psychological aspect of this symptom may not be routinely taken into account in ICU. Of note of the sensation of breathlessness was more closely correlated with swallowing dysfunction than with decrease in VC.

In conclusion, the current study has shown that, in patients with GBS, anxiety is at admission often intense, increased by presence of bulbar dysfunction, focused on intubation and definitive paralysis and, when accompanied by feeling of uncertainty, independently associated with subsequent requirement of MV. These results indicate that early management of patients with GBS should evaluate anxiety and assess its causes not only for psychologically ease the patients but also anticipate subsequent deterioration. Although these findings need to be confirmed in a larger and multicentre cohort, it is the first study demonstrating that anxiety, often considered too subjective by physicians, possesses an objective and prognosis value that could be helpful in orientating patients. It would be of interest to determine in what extend anxiety is a marker of immediate or future severity in other disease than GBS.

Acknowledgements This manuscript is dedicated to Professor Jean-Claude Raphaël.

Contributors TS conceived, designed and developed the study protocol, interpreted the results and wrote the first draft of the manuscript. TM helped with recruitment of the patients and collecting of the data. MB performed psychological tests and participated in the interpretation of the data. RP conceived and performed all the statistical analyses, interpreted the results and participated in the drafting and revision of the manuscript. AP helped with recruitment of the patients and collecting of the data. MA helped with the recruitment of the patients and collecting of the data. M-CD performed all the electrophysiological testing. DO helped with the recruitment of patients. DF helped with the recruitment of patients. DA participated in the revision of the manuscript M-HM performed psychological test, participated in the study design and interpretation of the data.

Competing interest None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement None.

REFERENCES

- Association AP. *Diagnostic and statistical manual of mental disorders*. 2000 edn, Washington, DC. 2000.
- Weiss H, Rastan V, Mullges W, *et al*. Psychotic symptoms and emotional distress in patients with Guillain-Barre syndrome. *Eur Neurol* 2002;47:74–8.
- Durand MC, Prigent H, Sivadon-Tardy V, *et al*. Significance of phrenic nerve electrophysiological abnormalities in Guillain-Barré syndrome. *Neurology* 2005;65:1646–9.
- Durand MC, Porcher R, Orlikowski D, *et al*. Clinical and electrophysiological predictors of respiratory failure in Guillain-Barré syndrome. *Lancet Neurol* 2006;5:1021–8.
- Lawn ND, Fletcher D, Henderson RD, *et al*. Anticipating mechanical ventilation in Guillain-Barre syndrome. *Arch Neurol* 2001;58:893–8.
- Hahn AF. The challenge of respiratory dysfunction in Guillain-Barre syndrome. *Arch Neurol* 2001;58:871–2.
- Sharshar T, Chevret S, Bourdain F, *et al*. Early predictors of mechanical ventilation in Guillain-Barre syndrome. *Crit Care Med* 2003;31:278–83.
- Strauss J, Aboab J, Rottmann M, *et al*. Plasma cortisol levels in Guillain-Barre syndrome. *Crit Care Med* 2009;37:2436–40.
- Walgaard C, Lingsma HF, Ruts L, *et al*. Prediction of respiratory insufficiency in Guillain-Barre syndrome. *Ann Neurol* 2010;67:781–7.
- Orlikowski D, Sharshar T, Porcher R, *et al*. Prognosis and risk factors of early onset pneumonia in ventilated patients with Guillain-Barre syndrome. *Intensive Care Med* 2006;32:1962–9.
- Fletcher DD, Lawn ND, Wolter TD, *et al*. Long-term outcome in patients with Guillain-Barre syndrome requiring mechanical ventilation. *Neurology* 2000;54:2311–15.
- Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. *Ann Neurol* 1990;27(Suppl):S21–4.
- Spielberger CD, Gorsuch RC, Lushene RE. *Manual for the state trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press, 1970.
- Sepulcri RP, do Amaral VF. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2009;142:53–6.
- Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. *J Infect Dis* 1997;176(Suppl 2):S92–8.
- Hadden RD, Cornblath DR, Hughes RA, *et al*. Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. *Ann Neurol* 1998;44:780–80.
- Hughes RA, Wijdicks EF, Benson E, *et al*. Supportive care for patients with Guillain-Barré syndrome. *Arch Neurol* 2005;62:1194–8.
- Ropper AH, Kehne SM. Guillain-Barre syndrome: management of respiratory failure. *Neurology* 1985;35:1662–5.
- Wijdicks EF, Borel CO. Respiratory management in acute neurologic illness. *Neurology* 1998;50:11–20.
- Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;165:710–18.
- Everitt B. *An R and S-PLUS companion to multivariate analysis*. In: Springer, London, England, 2005.
- Team TRDC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2009.
- Chevret S, Deléamont P. Repeated vital capacity measurements as predictive parameters for mechanical ventilation need and weaning success in the Guillain-Barré syndrome. *Am Rev Respir Dis* 1991;144:814–18.
- Jiang W, Kuchibhatla M, Cuffe MS, *et al*. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004;110:3452–6.
- Szekely A, Balog P, Benko E, *et al*. Anxiety predicts mortality and morbidity after coronary artery and valve surgery—a 4-year follow-up study. *Psychosom Med* 2007;69:625–31.
- Uyarel H, Kasikcioglu H, Dayi SU, *et al*. Anxiety and P wave dispersion in a healthy young population. *Cardiology* 2005;104:162–8.
- Detroyer E, Dobbels F, Verfaillie E, *et al*. Is preoperative anxiety and depression associated with onset of delirium after cardiac surgery in older patients? A prospective cohort study. *J Am Geriatr Soc* 2008;56:2278–84.
- Schmidt M, Demoule A, Polito A, *et al*. Dyspnea in mechanically ventilated critically ill patients. *Crit Care Med* 2011;39(9):2059–65.
- Khan F, Pallant JF, Ng L, *et al*. Factors associated with long-term functional outcomes and psychological sequelae in Guillain-Barre syndrome. *J Neurol* 2010;257:2024–31.