RELEVANCE OF ANXIETY IN CLINICAL PRACTICE OF GUILLAINBARRE SYNDROME: A COHORT STUDY

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000893
Article Type:	Research
Date Submitted by the Author:	22-May-2012
Complete List of Authors:	Sharshar, Tarek; R.Poincaré Hospital, Intensive Care Unit Polito, Andrea; R.Poincaré Hospital, Intensive Care Porcher, Raphael; Saint-Louis Teaching Hospital, Biostatistics and Medical Computer Science Department Meharbene, Takoua; R.Poincaré Hospital, Intensive Care Unit Blanc, Morgane; R.Poincaré Hospital, Intensive Care Unit Antona, Marion; R.Poincaré Hospital, Intensive Care Unit Durand, Marie-Christine; R.Poincaré Hospital, Functional Testing Department Friedman, Diane; R.Poincaré Hospital, Intensive Care Unit orlikowski, david; R.Poincaré Hospital, Intensive Care Unit Annane, Djillali; R.Poincaré Hospital, Intensive Care Unit Marcadet, Marie-Hélène; R.Poincaré Hospital, Intensive Care Unit
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Neurology, Mental health, Respiratory medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neuromuscular disease < NEUROLOGY, Anxiety disorders < PSYCHIATRY

RELEVANCE OF ANXIETY IN CLINICAL PRACTICE OF GUILLAIN-BARRE SYNDROME: A COHORT STUDY

TAREK SHARSHAR [*], ANDREA POLITO[*], RAPHAËL PORCHER[#], TAKOUA MEHARBENE[*], MORGANE BLANC, MARION ANTONA[*], MARIE-CHRISTINE DURAND[¶], DIANE FRIEDMAN[*], DAVID ORLIKOWSKI[*], DJILLALI ANNANE[*], MARIE-HÉLÈNE MARCADET [*]

[*] Medical Intensive Care Unit, Raymond Poincaré Teaching Hospital, 104 boulevard Raymond Poincaré, 92380 Garches, France

[#] Biostatistics and Medical Computer Science Department, Saint-Louis Teaching Hospital, 1 rue Claude Vellefaux, 75010, Paris, France

[¶] Functional Testing Department, Raymond Poincaré Teaching Hospital, 104 boulevard Raymond Poincaré, 92380 Garches, France

Corresponding author: Tarek Sharshar MD, PhD - Hôpital Raymond Poincaré - Service de Réanimation Médicale - 104, boulevard Raymond Poincaré - 92380 Garches - France

Tel: (33) 1 47 10 77 80

Fax: (33) 1 47 10 77 83

E-mail: tarek.sharshar@rpc.aphp.fr

Keywords : Guillain-Barre, Neuromyopathy, Anxiety, Uncertainty, Mechanical Ventilation

Words count: 3311

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 to 77) and anxiety VAS 5.2 (range 0 to 10). STAI was above 60/80 in 22 (21%) patients and anxiety VAS above 7/10 in 28 (27%) patients. Fear of remaining paralyzed, 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 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 disease[2] characterized 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 is required in about 20 percent 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 seven days [7 9], inability to lift the head [7], bulbar dyfunction [5] , vital capacity less than 60% of predictive value [7], plasma cortisol level [8] 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 GBS [12]and were not mechanically ventilated before or within 24 hours 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 dyspnea

Within 24 hours 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; 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 dyspnea 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 mechanical ventilation, 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 mechanical ventilation, 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 minutes and was done after neurological examination and VC measurement. We considered severe anxiety when STAI-Y1 was above 60 [14] or VAS-anxiety above 7.

Clinical and laboratory variables

The following data were recorded: 1) pre-GBS events such as diarrhea; 2) time from motor symptom onset to admission; 3) severity of muscle weakness assessed using the disability grade and arm grade [15] (Table 1); 4) presence of sensory loss; 5) inability to lift the head, bulbar dysfunction, and facial palsy; 5) cerebrospinal fluid parameters; 6) liver function tests. It was also noticed the patient was sent from emergency room, neurology department or other unit. Slow inspiratory VC was measured in triplicate using a spirometer (Morgan; United Kingdom), with the patient seated with the back reclined at 30° to 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 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 minutes. Biological tests were done at 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 hours after admission.

Follow-up

Criteria for mechanical ventilation

The decision to use mechanical ventilation was left at the discretion of the physician in charge of the patient. However, mechanical ventilation (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) $PaCO_2 > 6.4$ kPa, (3) $PaO_2 < 7.5$ 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]. Mechanical ventilation was always invasive.

The physicians who decided to start MV were unaware of the results of anxiety tests (including VAS dyspnea). In all patients who required MV, the time from inclusion to MV was longer than 12 hours. 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 (e.g., plasma exchange or intravenous immunoglobulin) were recorded and were left at physician's discretion. Disability grade was also assessed at six months.

Statistical analyses

Qualitative variables are presented as number (percent) and continuous variables as mean (standard deviation - SD) or median (interquartile range - 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% confidence interval, 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, vital capacity 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 mechanical ventilation [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 5 events in the models, as this showed to maintain comparable reliability as models with 10 to 16 events per variable [20 21]. We thus selected a set of factors associated with subsequent mechanical ventilation 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 version 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. 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%) 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 to 77) and 5.2 (range 0 to 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 paralyzed, 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 2. Arm grade and presence of bulbar dysfunction correlated with STAY-Y1 and GBS specific questionnaire score. Female gender and disability grade correlated with STAY-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 r other department. Mean value of anxiety tests did not statistically differ between psychologists (MHM and MB) and by non-psychologists evaluators.

Relationships between anxiety and subsequent mechanical ventilation

25 (23%) patients required MV, at a median time of 3 days after inclusion (range 1 to 14 days). At inclusion, patients who subsequently required MV had greater limb weakness (manifesting as worse disability and arm grades, P=0.001 and P=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 dyspnea 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).

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 paralyzed, being intubated and not knowing how their condition would progress.

It is interesting to note that it was not the intensity of anxiety, evaluated with various scores (i.e. STAI-Y1, GBS specific score, VAS), but its object, i.e. uncertainty, that was most strongly associated with respiratory failure. This finding raises two issues. Firstly, 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 per cent 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 in what extend. 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. Vital capacity (VC), one of the most powerful predictors, was not

significantly different between patients who did or did not subsequently require MV [3-8 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 [3-8 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 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 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 since most patients have already received some information about GBS before being admitted to ICU and are therefore 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 pre-operative 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 paralyzed, about needing

to be intubated and about not knowing how the disease will progress, indicating areas which psychological support should be focused on. Finally, 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 dyspnea, 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 minutes. 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 mechanical ventilation vary according to the

stage of GBS course, and importantly that subjective symptoms (i.e. anxiety, uncertainty, breathlessness) may precede objective signs (i.e. weakness, decreased VC, cortisol etc…), as depicted in Figure 1.

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 six years after their discharge from neuro-ICU. Therefore, these two studies have assessed anxiety during the stay and after discharge from the ICU, respectively, whereas the present study have 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 finding need to be confirmed in a larger and multicenter 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.

REFERENCES

1. Association AP. Diagnostic and Statistical Manual of Mental Disorders. 2000 ed, 2000.
2. Weiss H, Rastan V, Mullges W, et al. Psychotic symptoms and emotional distress in patients with Guillain-Barre syndrome. Eur Neurol 2002;47(2):74-8.
3. Durand MC, Prigent H, Sivadon-Tardy V, et al. Significance of phrenic nerve electrophysiological abnormalities in Guillain-Barré syndrome. Neurology 2005;65:1646-49.
4. Durand MC, Porcher R, Orlikowski D, et al. Clinical and electropysiological predictors of respiratory failure in Guillain-Barré syndrome. Lancet Neurol 2006;5:1021-28.
5. Lawn ND, Fletcher D, Henderson RD, et al. Anticipating mechanical ventilation in Guillain-Barre syndrome. Arch Neurol 2001;58:893-98.
6. Hahn AF. The challenge of respiratory dysfunction in Guillain-Barre syndrome. Arch Neurol 2001;58(6):871-2.
7. Sharshar T, Chevret S, Bourdain F, et al. Early predictors of mechanical ventilation in Guillain-Barre syndrome. Crit Care Med 2003;31(1):278-83.
8. Strauss J, Aboab J, Rottmann M, et al. Plasma cortisol levels in Guillain-Barre syndrome. Crit Care Med 2009;37(8):2436-40.
9. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barre syndrome. Ann Neurol 2010;67(6):781-7.
10. 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(12):1962-9.
11. Fletcher DD, Lawn ND, Wolter TD, et al. Long-term outcome in patients with Guillain-Barre syndrome requiring mechanical ventilation. Neurology 2000;54(12):2311-5.

12. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol 1990;27 Suppl:S21-4.

13. Spielberger CD, Gorsuch RC, Lushene RE. Manual for the State Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.

14. Sepulcri Rde P, do Amaral VF. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol 2009;142(1):53-6.

15. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis 1997;176 Suppl 2:S92-8.

16. 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;44:780-38.

17. Hughes RA, Wijdicks EF, Benson E, et al. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol 2005;62:1194-98.

18. Ropper AH, Kehne SM. Guillain-Barre syndrome: management of respiratory failure. Neurology 1985;35(11):1662-5.

19. Wijdicks EF, Borel CO. Respiratory management in acute neurologic illness. Neurology 1998;50:11-20.

20. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165(6):710-8.

21. Everitt B. An R and S-PLUS companion to multivariate analysis. In: Verlag S, editor. London, 2005.

22. Team TRDC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2009.

23. Chevrolet JC, 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.

24. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation 2004;110(22):3452-6.

25. 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(7):625-31.

26. Uyarel H, Kasikcioglu H, Dayi SU, et al. Anxiety and P wave dispersion in a healthy young population. Cardiology 2005;104(3):162-8.

27. 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(12):2278-84.

28. Schmidt M, Demoule A, Polito A, et al. Dyspnea in mechanically ventilated critically ill patients. Crit Care Med 2011.

29. 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(12):2024-31.

Competing interest: The authors declare that they have no competing

Funding statement: There was no funding from any source for this research

Acknowledgement

This manuscript is dedicated to Professor Jean-Claude Raphaël.

Contributorship statement:

T. Sharshar conceived, designed and developed the study protocol, interpreted the results and wrote the first draft of the manuscript.

T. Meharbene helped with recruitment of the patients and collecting of the data

M. Blanc performed psychological tests and participated in the interpretation of the data

R. Porcher conceived and performed all the statistical analyses, interpreted the results and participated in the drafting and revision of the manuscript.

A. Polito helped with recruitment of the patients and collecting of the data

M. Antona helped with the recruitment of the patients and collecting of the data

M.-C. Durand performed all the electrophysiological testing

D. Orlikowski helped with recruitment of patients.

D. Friedman helped with recruitment of patients.

D Annane participated in the revision of the manuscript

M.-H. Marcadet performed psychological test, participated in the study design and interpretation of the data

LEGENDS

Legend of 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.

Abbreviations: VC: vital capacity; MV: mechanical ventilation; CPN: conduction block on peroneal nerve; onset-admission<7days: delay from onset to admission < 7 days.

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 to 9)	6 (4 to 9)	4 (2 to 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[1] (hours)	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)
Disability grade[2] > 3 (%)	42 (38)	25 (29)	17 (68)
Arm grade[3] > 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 to 20)	16 (14 to 20)	17 (15 to 20)
Saturation of peripheral oxygen (%)	98 (95 to 98)	97 (95 to 98)	98 (96 to 98)
CSF protein (g/L)	0.7 (0.5 to 1.14)	0.72 (0.52 to 1.14)	0.62 (0.47 to 0.99)
No anti-ganglioside Ab (%)	54 (49)	41 (48)	13 (52)
Liver dysfunction (%)	15 (14)	10 (12)	5 (20)
Demyelinating electrophysiology (%)[4]	25 (57)	19 (53)	6 (75)
Baseline plasma cortisol level (ng/ml)	181 (132 to 252)	180 (139 to 250)	181 (105 to 236)
Plasma exchange (%)	57 (32)	51 (60)	6 (24)

IvIg (%)	53 (48)	31 (36)	22 (88)
Time from inclusion to MV (days)			3 (2 to 4)

[1]Inclusion is time of anxiety assessment; In all patients who required MV, the time from inclusion to EMV was longer than 24 hours.

[2]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; 6, dead [15].

[3]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; 5, dead [15].

[4]Available in 66 (60%) patients

Decision for MV was based on presence of one major criterion or two minor criteria. Major criteria: (1) intolerable respiratory distress, (2) $PaCO_2 > 6.4$ kPa, (3) $PaO_2 < 7.5$ 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].

Abbreviations: GBS, Guillain-Barré Syndrome; MV, mechanical ventilation; N: number; IQR: Interquartile range; CSF: cerebrospinal fluid; CJ, Campylobacter jejuni; CMV, Cytomegalovirus, Ab, antibodies; VC: vital capacity; IvIg: intravenous immunoglobulin

Table 2 – Features of anxiety

Variable n (%) or **mean ± SD or median (IQR)**	**All patients** 110	**Non ventilated** 85	**Ventilated** 25
Preexisting 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 paralyzed	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)

Table 2 (followed) – Features of anxiety

Variable n (%) or **mean ± SD or median (IQR)**	**All patients** 110	**Non ventilated** 85	**Ventilated** 25
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 to 8)	5 (3 to 7)	5 (4 to 8)
Dyspnea-VAS (from 0 to 10)	2 (0 to 4)	1 (0 to 4)	4 (0 to 5)

Abbreviations: STAI-Y1 : State Trait Anxiety Inventory-Y1; GBS, Guillain-Barré Syndrome; CI: confidence interval; VASS : visual analogical scale.

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[1]	0.22	0.03 to 0.39	0.022	0.16	-0.03 to 0.34	0.095
Arm grade[2]	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[3]	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.

[1]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; 6, dead [15].

[2]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; 5, dead [15].

[3]Expressed as % of predicted value

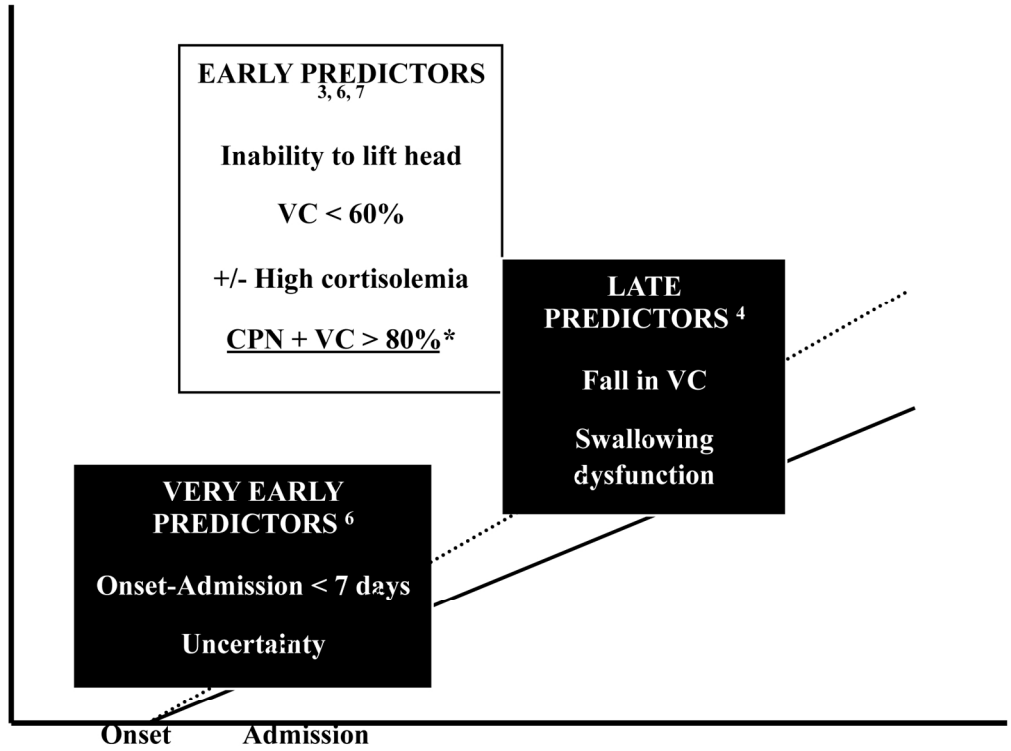
Abbreviations: GBS, Guillain-Barré Syndrome; CI: confidence interval; VA : visual analogical scale.

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

Variable	STAI-Y1[13]	GBS questionnaire	Anxiety-VAS	Dyspnea-VAS
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
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
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
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)	
Dyspnea-VAS score				1.28 (0.46 to 3.57
Uncertainty as most frightening				

[1]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; 5, dead [15].

Abbreviations: STAI-Y1: State Trait Anxiety Inventory-Y1; GBS, Guillain-Barré Syndrome; CI: confidence interval; VAS: visual analogical scale.



149x118mm (300 x 300 DPI)

Reviewer: 1

Comments to the Author

The paper reports a prospective study on the effect of anxiety on the outcome of GBS (ventilatory support). In a consecutive series of 105 patients, anxiety level (measured with 3 different rating scales) was relatively high and was related to the subsequent use of ventilator support.

The authors conclude that anxiety should be recognized and treated in GBS patients.

I have some questions:

1) There was a difference between the delay to admissions and the presence of anxiety?

Reply - We did not find any correlation between delay to admission and VAS-anxiety (r=-0.09 (-0.27 to 0.10), p=0.37), Dyspnea-VAS (r= -0.31 (-0.47 to -0.13), p=0.001) and uncertainty (r=0.03 (-0.23 to 0.29), p=0.84). This is now mentioned in the revised manuscript. As shown in Table 3, delay to admission was not correlated with STAI (r=-0.09 (-0.28 to 0.010), p=0.34) and GBS questionnaire (r=-0.002 (-0.19 to 0.18), p = 0.98).

2) Anxiety scores were correlated to a series of factors, such as disability score, bulbar dysfunction, etc. Could the authors also correlate anxiety with the progression rate of disability (a patient could be more anxious if the disease is more rapidly progressing). An analysis of this correlation would add important information to the paper.

Reply – As answered in the previous question, we did not find We did not find any correlation between delay to admission and VAS-anxiety, Dyspnea-VAS and uncertainty, delay to admission being a marker of progression rate. Indeed, delay to admission shorter less than 7 days has been shown to be predictive of subsequent respiratory failure (Sharshar et al Crit Care Med 2003). This is now mentioned in the revised manuscript.

Reviewer: 2

Comments to the Author

The authors have investigated the presence and significance of anxiety in 110 patients suffered of GBS and admitted in an ICU. Anxiety was evaluated at the admission time with two different scales and correlated, as predictor of mechanical ventilation, with other clinical and biologic parameters.

According a very accepted James Lange theory, emotions in general and fear in particular would be conscious perceptions of certain body changes, mediated fundamentally by vegetative nervous system. In spite the fact that in the present study there was no statistical correlation between anxiety scores and respiratory and rate, blood pressure and plasma cortisol levels, anxiety at admission was intense and, independently of other clinical and biologic parameters, associated with requirement of mechanical ventilation. The conclusion is clear: anxiety in patients with GBS must be early evaluated and considerate for patient management.

When an aware patient is admitted in an ICU, he always wants to know her clinical situation that´s determining the ICU admittance and also an initial evolution prognostic. Initial medical information and previous emotional and personality disturbances are important factors non evaluated in the work of Tarek et al: we don't know if those patients with GBS admitted in the RPT Hospital ICU were sent from the Emergency Service or from the Neurology Service and the quality of medical information received.

Reply - The origin (emergency room, neurology department or other department) is now provided. Unfortunately, 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 in what extend. The indirect arguments against such an influence are that the different origins differ neither for intensity of anxiety nor for incidence of respiratory failure. This is now mentioned in the revised manuscript.

We also don´t have any information about previous emotional disorders.
Reply - We do not agree as pre-existing psychological disorders (i.e. depression; anxiety etc…), uptake of anti-psychotic drugs (i.e. antidepressant, neuroleptic, anxiolytic…) and chronic alcoholism have been collected and presented in Table 2.

This study is an original investigation. Bibliographic references writing must be thoroughly revised. A final question: why in the abstract the number of included patients is 105 and 110 in the figure 1?
Reply - It is an error. 110 patients have been included. The abstract has been corrected.

Reviewer: 3
Comments to the Author
Sharshar T et al reported that anxiety in GBS patient is associated with subsequent mechanical ventilation, in addition to those reported so far.

This paper is a laborious work, however, uncertainty seems obscure to some extent. I do not understand the difference between uncertainty and anxiety. I think that the anxiety or uncertainty is dependent on inherent stress tolerance of each patient.
Reply - Anxiety and uncertainty are different, although linked. There are different reasons to be anxious. Certainly, uncertainty is major anxiogenic factor, especially in a disease whose course is not easily predictable, but it is not the only one. We thought that intensity of anxiety should be evaluated but also its object (i.e. of what the patient is anxious). This is why we have asked the patients if his anxiety was mainly explained by uncertainty, pain, breathlessness or weakness and we have developed the GBS questionnaire.

Besides, I wonder that same information about the progression of GBS is given to each patient in this study.
Reply - Although As stated in the methods section, we acknowledged the information about the diagnosis and progression of GBS from the physician could have had the effect of increasing or decreasing anxiety. As mentioned, "*the information was given by the physician in charge of the patient. 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 mechanical ventilation, despite plasma exchanges or infusion of high-dose of intravenous immunoglobulin (IvIg). All physicians had clinical experience with GBS patients and specific training on its pathophysiology, clinical course and treatment*".
Therefore, we are convinced that information was similar among patients.
Moreover we have discussed some arguments that are against an influence by physician's information. *First, vital capacity (VC), one of the most powerful predictors, was not significantly different between patients who did or did not subsequently require MV. 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. 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 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.
However, we "tempered" these statements by writing that *"Despite these arguments, we acknowledge that we are not able to determine in what extent medical information might have influenced patient responses. Assessment of 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 since most patients have already received some information about GBS before being admitted to ICU and are therefore not naïve"*.

Minor criticisms

1. Which is the correct number of patients included in this study, 105 (abstract) or 110 (text and table) ?

Reply - 110 patients have been included.

2. There are two periods in the last sentence in Page 13.

Reply -This is now corrected.

3. There are no explanations for abbreviations (VC and MV) in the abstract.

Reply - These abbreviations are now explained in the abstract.

4. Although authors had carried out electrophysiological study and measurement of serum anti-ganglioside antibodies, these data are not shown in this paper. There are some reports saying the relationship between anti-gangloside antibodies and respiratory failure in GBS patients.
Reply-These data are now provided. There was no difference between ventilated and non-ventilated patients in terms of anti-ganglioside antibodies.

Reviewer: 4
Comments to the Author

1. The title should state that anxiety may have significance on clinical practice in the acute phase, that is what has been investigated.

Reply - This is now stated in the title.

2. Abstract. Spell out abbreviations such as STAY-Y1., VC and MV.

Reply - These abbreviations are now spelled out in the abstract.

3. Please give a definition of anxiety.

Reply - A definition of anxiety is now given in the introduction. It originates from DSMIV.

4. In the introduction give definition of anxiety. The authors state that GBS is a very anxiogenic disease and refer to only one study. Please refer to more studies to support that statement.

Reply - We have referred to more studies but also to the textbook on Guillain-Barré syndrome edited by Allan Ropper. All these documents indicate that anxiety is frequent in the acute phase of Guillain-Barré syndrome.

Otherwise the introduction is short and provides an overview of the studied area.

5. Aim is clear.
Reply - Thanks.

6. Baseline parameters. The patients were assessed with several measures. In which order was the measures performed? Both rating scales and physical measures were used, in which order were they performed? Were all measures performed at the same time? The patients were all very ill, are the results of all these measures reliable as the patients probably got tired? How long time did all these measures take? It seems like there were several evaluators, the authors should discuss inter-rater reliability of the VAS and STAI-Y1.
Reply - Neurological examination (with interview of the patient) and measurement of vital capacity (VC) were first done, taking less than 30 minutes. Biological tests were done at 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 (there is no emergency to do it).
Evaluation of anxiety took about 15 minutes and was done after neurological examination and VC measurement. This order is mentioned in methods section.
The entire clinical examination took less than 45 minutes. 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.
We have not assessed inter-rater reliability of STAI-Y1 and VAS. As mentioned in the methods, "a*ll 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*". This training and standardizing are likely to have reduced inter-rater variability.

6. Follow-up. Who performed the follow-up? The same investigators who performed baseline? Intra-rater reliability should be discussed.
Reply - Follow-up consists of collecting data that are recorded in routine by the physicians, nurses and physiotherapists in charge of the GBS patients.

7. Statistical analyses. Why was the Somers Dxy rank correlation coefficients used? Correct for multiple statistical comparisons. The authors have performed several comparisons between ventilated and non-ventilated patients and some significance is probably by chance.
Reply - Somers Dxy correlation coefficient was used because it is well-suited to quantify the correlation between a binary variable and a quantitative variable. It is expressed the same way as a Pearson or a Spearman correlation coefficient, with the same range of values (i.e. between -1 and 1). This allowed an unformed reporting of results for quantitative and binary variables.
We also agree that many comparisons were performed between ventilated and non-ventilated patients, and some factors may have been found significant by chance. But the purpose of these comparisons was not to have definite conclusions regarding the different predictors of MV, but rather to select the potential confounder on which to adjust the analysis of anxiety features. We thus feel that these analyses should not be penalized for multiplicity. Concerning the anxiety features, five variables were tested in table 4, after adjustment for potential confounders. If the number of patients (and events) was larger, we would have performed a

more usual multivariable analysis, and sequentially deleted the factors not associated with MV. Unfortunately, using a logistic model with five or six predictors was not reasonable here. But we however chose to present only adjusted analyses, to remove confounding as possible. Another strategy would be to first perform unadjusted tests of association of MV with these features, while correcting for multiple testing. We would thus obtain p-values of 0.044 for STAI-Y1, 0.041 for GBS questionnaire, 0.41 for anxiety VAS, 0.044 for dyspnea VAS and 0.041 for uncertainty as most stressful, after correction to control a false discovery rate of 5% (Benjamini and Hochberg 1995). On the basis of these results, adjusted analysis of anxiety VAS would not be performed. However, the conclusions would not be changed. The obtained odds-ratios for GBS questionnaire and most stressful are very wide. If an association by chance is quite unlikely (given what we have detailed above, and the odds-ratios values), an over-optimistic strength of association is very plausible.

8. Results. References to the used cut-off score of the STAI and VAS are needed?
Reply - A value of 60 corresponds to the last quartile of the STAI whose maximum is 80. In a previous study (Rodrigo de P. Sepulcri and Vivian F. do Amaral, European Journal of Obstetrics and Gynecology and Reproductive Biology, 2009), anxiety was considered when STAI value was above 52. For this reason, to be sure to have a real anxious population, we have considered 60 the anxiety cut-off for STAI. There is no reference for VAS above 7/10.

9. Discussion. The correlation coefficients were only moderately between the VAS score and STAI, discuss possible reasons for that in the discussion. The confidence interval for the STAI score for patients subsequently requiring mechanical ventilation was wide indicating, discuss that. The discussion should be shortened.
Reply – The issue on confidence interval is addressed in the reply for question 7.
The addressing of the issues raised by the reviewers hampered us to shorten the discussion. If the reviewer or the editor would request so, we will be ready to remove part of the discussion that they do not consider necessary.

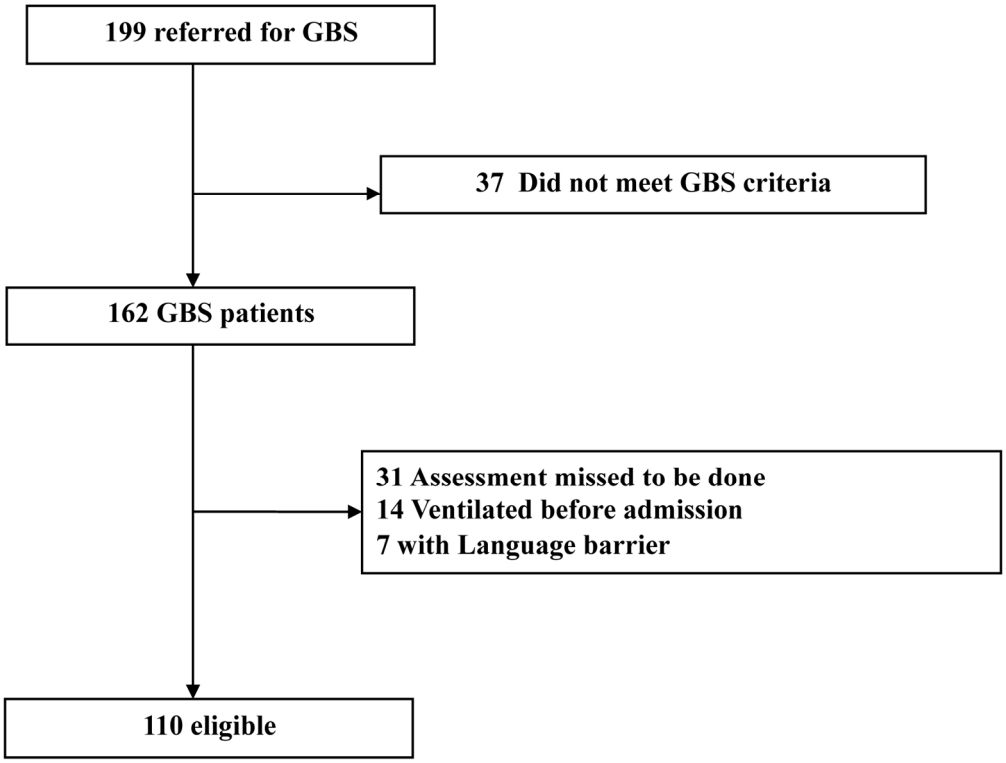
References: Omit reference 5.
Reply - It is now done

Figures and tables:
Omit Figure 1 and 2 as the same information is in the text.
Reply - The figures 1 and 2 have been deleted (and put in online supplement file).

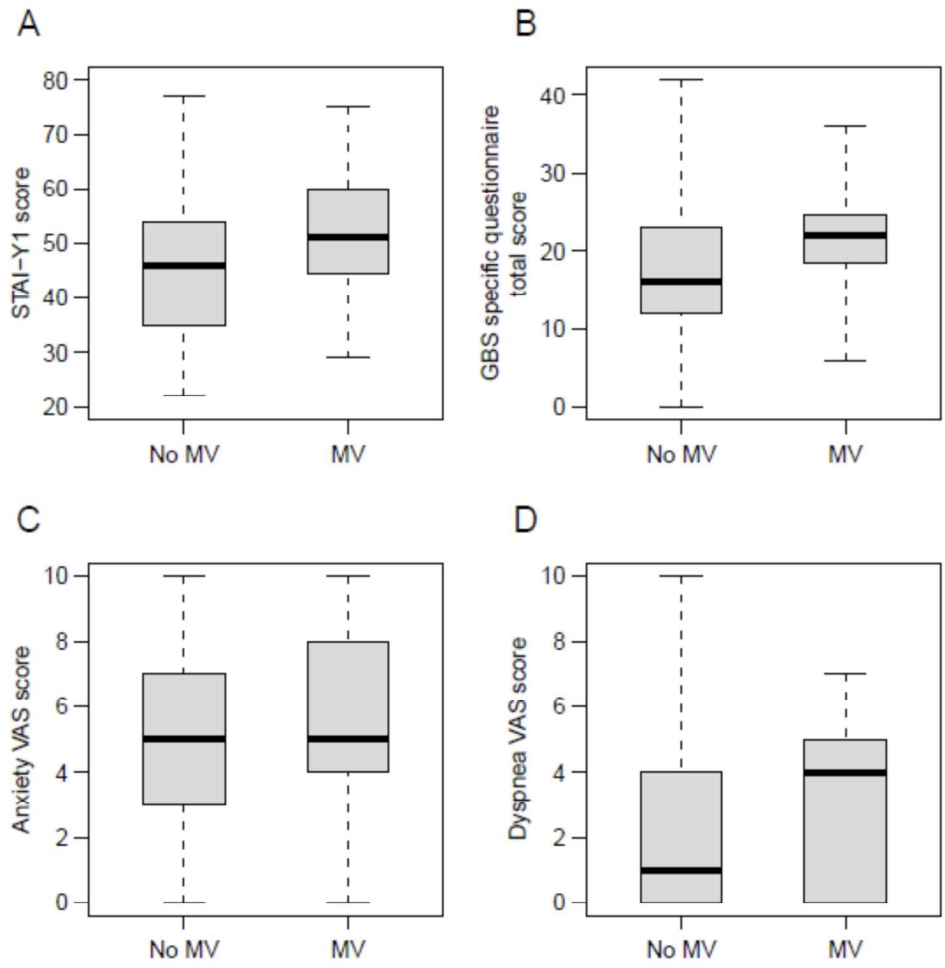
RELEVANCE OF ANXIETY IN CLINICAL PRACTICE OF GUILLAIN-BARRE SYNDROME (Supplementary File)

Legend of figure 1. Numbers of screened, excluded and included patients are stated. Abbreviation: GBS, Guillain-Barré Syndrome

Legend of Figure 2. Evaluation of anxiety within the 24 hours of admission in relation to subsequent MV. The box plots display the median (thick line) and the first and third quartiles (box) of the distribution, and outer whiskers span the whole range of data.



150x115mm (300 x 300 DPI)



150x153mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 and 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9
		(*e*) Describe any sensitivity analyses	8-9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl mat
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	9-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.