Pain during the acute phase of Guillain–Barré syndrome

Shaoli Yao, MDa, Hongxi Chen, MDa, Qin Zhang, MDa, Ziyi Shi, PhDa, Ju Liu, PhDa, Zhiyun Lian, PhDa, Huiru Feng, MDa, Qin Du, MDa, Jinlu Xie, MDa, Weihong Ge, BDb, Hongyu Zhou, PhDc,∗

Abstract

In this study, we tried to describe the characteristics of pain and explore the association between the incidence of pain and abnormal laboratory test results in patients during the acute phase of Guillain–Barré syndrome (GBS).

This retrospective cohort study enrolled 252 patients with GBS who were in the acute phase of the disease. We collected data regarding the location and type of pain, the onset time, clinical variables and laboratory tests, including the levels of uric acid (UA), albumin, cerebrospinal fluid protein (CSFP), cerebrospinal fluid glucose (CSFG), fasting glucose upon admission, and blood creatinine. The pain descriptors were compared to the severity of disease and laboratory examination results.

Around 34.5% of the patients reported pain during the acute phase of GBS. Pain was negatively correlated with the disease severity during the acute phase. In total, 29 of the 87 (33.3%) patients reported pain during the 2 weeks preceding the onset of weakness. The concentration of CSFP was positively associated with the incidence of pain, while the concentrations of UA and albumin were not correlated with the incidence of pain.

We found that 33.3% of the GBS patients experienced pain within 2 weeks of onset, and the pain was positively associated with CSFP concentration but was not correlated with disease severity.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CSFG = cerebrospinal fluid glucose, CSFP = cerebrospinal fluid protein, GBS = Guillain–Barré syndrome, MS = multiple sclerosis, NMO = neuromyelitis optica, UA = uric acid.

Keywords: albumin, cerebrospinal fluid protein, Guillain–Barré syndrome, pain, uric acid

1. Introduction

Guillain–Barré syndrome (GBS) is an immune-mediated inflammatory peripheral neuropathy that is characterized by acute progressive motor weakness and areflexia.[1] Clinicians often focus on the motor weakness because it may severely influence patients’ ability of daily life. Recently there has been an increased interest in sensory symptoms associated with GBS, especially the pain, because of its impact on quality of life. Several studies have focused on the management of pain in GBS.[2,3] Only 5 studies investigating pain in GBS patients with long-term following up. The reported frequency of pain in GBS is highly variable (53%–89%), and the intensity of the pain ranges from moderate to severe.[4–8] Nevertheless, the relationship between disease severity and pain is controversial. Some studies indicated that there was no significant correlation between disability and pain intensity.[4] Whereas others studies demonstrated that pain was associated with long-term disability in GBS patients.[5,9] A lot of literature suggested that excessive production of the reactive oxygen species or reactive nitrogen species that led to oxidative and nitrosative stress was the major determinant in the pathogenesis of inflammatory and autoimmune diseases of the nervous system.[10] Uric acid (UA) is known as a scavenger of peroxynitrite.[11] Several studies demonstrated that peroxynitrite is implicated in the immunopathogenesis of immune-related diseases.[12,13] UA is a naturally occurring antioxidant with metal-chelating properties[14] and accounts for up to 60% of the free radical scavenging activity in human blood.[15] Some studies confirmed that serum albumin had antioxidant properties and plays a major known antioxidant role in extracellular fluids.[16] As a result, UA and albumin associate with oxidative stress in some ways. GBS, neuromyelitis optica (NMO), and multiple sclerosis (MS) were all the inflammatory demyelinating autoimmune diseases of the nervous system and they had much in common in the pathogenesis. Lower serum UA and albumin levels were observed in patients with NMO[15,17,18] and GBS[19] than the health control groups. The association between UA, albumin, cerebrospinal fluid indexes, and pain remains unclear; thus, the current study was performed to address these issues.

2. Patients and methods

2.1. Patients

The inclusion criteria were as follows: patients fulfilling the diagnostic criteria for GBS[20] who were admitted to the Department of Neurology, West China Hospital, Sichuan University from September 2009 to August 2016. All enrolled patients were fulfilling the following criteria: rapid progression

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a Department of Neurology, West China Hospital, Sichuan University.

b Department of Internal Medicine, Hospital of Chengdu Office of People’s Government of Tibet Autonomous Region.

c Department of Neurology, West China Hospital, Sichuan University, China.

∗Correspondence: Hongyu Zhou, Department of Neurology, West China Hospital, Sichuan University, China (e-mail: zhouhy@scu.edu.cn).

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of more than one limb weakness with loss of tendon jerks; cerebrospinal fluid examination indicated the separation of protein and cells after the first week of symptoms; electrodiagnostic examination indicated nerve conduction was slow or blocked, or F-wave responses decreased; patients with ≤3 weeks between the symptom onset and admission time; and patients who were older than 14 years. The exclusion criteria were as follows: patients with coma and had communication difficulty; patients who presented with chronic pain for 3 months prior to the onset of GBS; patients with liver disease, abnormal ranges of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, as well as with renal failure. The data, including the demographic characteristics, history of diabetes, clinical symptoms and signs, Hughes score at nadir, the onset of pain, the type and location of pain, and medical treatment for GBS were collected. Of the 259 GBS patients, 6 were excluded due to coma and communication difficulty, and 1 patient was excluded due to the presence of chronic pain 3 months prior to the onset of GBS. Of the 252 patients enrolled, 87 patients had the complain of pain (Fig. 1).

The Hughes functional grading scale was used to evaluate the severity of the patients’ disabilities. The limb muscle strength was classified from 0 to 5 according to the criteria of the medical research council. Patients with a Hughes functional grading scale at nadir ≥3 points were defined as having severe GBS. Patients with a Hughes functional grading scale at nadir <3 points were defined as having mild GBS.

More than 80% GBS patients reach the nadir of weakness within 3 weeks of GBS onset. The first 3 weeks after the onset of the disease constitute the acute phase. Before beginning any treatment on admission, venous blood was collected in the morning after an overnight fast using an automatic analyzer.
was performed to examine the association between pain and the serological and cerebrospinal fluid indexes.

### 3. Results

In total, 252 GBS patients were enrolled in this study. The baseline and clinical characteristics of all enrolled patients are shown in Table 1. The male-to-female ratio was approximately 1.3:1. 159 (63.1%) patients exhibited cranial nerve involvement, and 171 (67.9%) patients were diagnosed with severe GBS. Of the 252 patients, 87 (34.5%) complained of pain and 53 (61.0%) of them were during the first 2 weeks following the onset of weakness. In total, 40 of the 87 (46.0%) patients reported 2 or more pain locations. Radicular pain (29.9%) and muscle pain (26.9%) were the most common types of pain reported by the GBS patients. The characteristics of the 87 patients who reported pain are shown in Table 2.

Spearman’s correlation analysis was performed to show that the pain was negatively correlated with the severity of the disease ($r_s = -0.152$, $P = .016$). After adjusting for age, gender and history of diabetes, pain was also negatively correlated with the severity of the disease ($\beta = -0.323$, $P = .035$). These data were shown in Table 3.

#### 2.2. Statistical analysis

All statistical analyses were performed using STATA version 12.1. Two-tailed $P$-values $<0.05$ were considered statistically significant. Normally distributed data are expressed as the mean ± standard deviation, and non-normally distributed data are expressed as medians (interquartile range). To examine the association between the disability of the GBS patients and pain, Spearman’s correlation analysis was performed, and a multiple linear regression was performed to correct for age, gender and history of diabetes. The comparisons of the concentrations of UA and albumin between the pain group and the nonpain group were performed using Student’s $t$-tests. The comparisons of the concentrations of CSFP between the pain group and the nonpain group were performed using a rank sum test. A logistic regression

### Table 1
Baseline and clinical characteristics of 252 patients in the acute phase of GBS.

| Values | GBS categories, n (%) | Pain, n (%) | Male, n (%) | Age (mean±SD) |
|--------|-----------------------|-------------|-------------|---------------|
| ADSP   | 233 (92.5)            | 74 (84.7)   | 113 (50.0)  | 50.27±18.06   |
| MFS    | 8 (3.2)               | 4 (4.6)     | 4 (1.7)     | 48.3±13.7     |
| AMAN   | 8 (3.2)               | 6 (6.9)     | 6 (2.4)     | 48.3±13.7     |
| Others | 3 (1.1)               | 1 (1.2)     | 2 (0.8)     | 49.0±13.6     |

### Table 2
Pain characteristics of 87 patients in the acute phase.

| Values | Baseline | GBS categories, n (%) | Male, n (%) | Pain, n (%) | Male, n (%) | Age (mean±SD) |
|--------|----------|-----------------------|-------------|-------------|-------------|---------------|
| ADSP   | 233 (92.5) | 74 (84.7) | 113 (50.0) | 50.27±18.06 | 74 (84.7) | 113 (50.0) | 50.27±18.06 |
| MFS    | 8 (3.2) | 4 (4.6) | 4 (1.7) | 48.3±13.7 | 4 (4.6) | 4 (1.7) | 48.3±13.7 |
| AMAN   | 8 (3.2) | 6 (6.9) | 6 (2.4) | 48.3±13.7 | 6 (6.9) | 6 (2.4) | 48.3±13.7 |
| Others | 3 (1.1) | 1 (1.2) | 2 (0.8) | 49.0±13.6 | 1 (1.2) | 2 (0.8) | 49.0±13.6 |

### Note

1. ADSP = acute inflammatory demyelinating polyneuropathy, AMAN = acute motor axonal neuropathy, GBS = Guillain–Barré syndrome, MFS = Miller–Fisher syndrome, Ig = immunoglobulin.
2. Sensory disturbances = abnormal vibration sense/pinprick.
3. Severe affected = unable to walk unaided. HFGS at nadir ≥ 3.
4. Given percentages are based on the number of patients without a history of hypertension.

### Note

1. The interpretation of pain is based on the case description.
2. Visceral pain refers to abdominal pain that could not be localized.
3. Severe affected = unable to walk unaided. HFGS at nadir ≥ 3.

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(Vitors 5600) to measure the serum concentrations of UA, albumin, fasting glucose, ALT, AST, and blood creatinine in the Clinical Laboratory of the West China Hospital of Sichuan University. In total, 215 patients received lumbar punctures during the acute phase; therefore, the concentrations of cerebrospinal fluid protein (CSFP) and cerebrospinal fluid glucose (CSFG) were also determined using the same analyzer. Patients were divided into group with pain and group without pain to compare the differences in the serological and cerebrospinal fluid indexes. This study was approved by the Ethics Committee of West China Hospital of Sichuan University.
The correlations between the serological and cerebrospinal fluid indexes and the incidence of pain were listed in Table 4. No significant differences were observed in the incidence of pain and the serum levels of UA and albumin ($P = .8505$, $P = .1693$, respectively) between the group with pain and the group without pain. However, the incidence of pain was associated with the concentration of CSFP ($P = .0074$). A logistic regression was performed to examine the association between pain and the serological and cerebrospinal fluid indexes (Table 5). The CSFP concentration was positively correlated with the incidence of pain ($\beta = 0.424$, $P = .024$).

### Table 3

| Variables     | Beta  | $P$-value | 95% CI |
|---------------|-------|-----------|--------|
| Pain          | -0.323| .035      | -0.622--0.023 |
| Gender        | -0.180| .218      | -0.466--0.107 |
| Age           | 0.010 | .015      | 0.002--0.018  |
| Diabetes      | -0.014| .958      | -0.525--0.498 |

Beta = standardized regression coefficient; CI = confidence interval.

### Table 4

| Comparison of the serological indexes and CSFP concentrations between the pain and nonpain groups. |
|---------------------------------------------------------------|
| Variables          | $P$ | $P^2$ |
|---------------------|-----|-------|
| Serological indexes |     |       |
| UA                  | .8505| .695  |
| Albumin             | .1693| .256  |
| CSFP concentration  | .0074|       |

CSFP = cerebrospinal fluid protein; $P^2$ = adjusted for age and gender; UA = uric acid.

### Table 5

| Logistic regression results of pain levels in GBS patients and laboratory examinations. |
|---------------------------------------------------------------------------------------|
| Variables     | Beta  | $P$-value |       |
|---------------|-------|-----------|-------|
| Gender        | 0.066 | .855      |       |
| Age           | -0.005| .616      |       |
| UA            | 0.000 | .946      |       |
| Albumin       | 0.037 | .286      |       |
| CSFG          | -0.253| .142      |       |
| CSFP          | 0.424 | .024      |       |

Beta = standardized regression coefficient, CSFG = cerebrospinal fluid glucose, CSFP = cerebrospinal fluid protein, GBS = Guillain–Barré syndrome, UA = uric acid.

was shown to be associated with the level of weakness, fatigue, and functional disability during the later stages of GBS but not the acute stage. In our study, pain was negatively correlated with the disability of patients during the acute phase. Although the exact reason for this finding was unclear, we hypothesize that the following reasons may be involved. Firstly, the degree of GBS severity was primarily based on the degree of muscle strength and paralysis in the patients, and the patients’ sensory symptoms tend to be ignored. Secondly, the pathogenesis of GBS may be different in patients with obvious symptoms; and thirdly, pain may serve as a warning signal, leading patients to visit a doctor. After experiencing pain, the patients visited the hospital, which might allow the earlier detection of the disease, timely treatments, and a possible reduction in the proportion of severe GBS patients.

This study was the first to report that the incidence of pain is positively correlated with the concentration of CSFP. The elevated CSFP concentrations would likely stimulate nerve root inflammation and influence afferent sensory nerves, and nerve inflammation could also cause elevated CSFP levels. It was a retrospective study that might have some defects in the data collection, statistical errors may have occurred in this study, and further prospective studies with larger sample sizes are required to confirm these results. In addition, we found that the most frequent pain location was the lower limbs, followed by the lower back and back, which was consistent with a previous study.

Often, more than one location was indicated among the patients with pain. In total, 40 of 87 (46.0%) patients reported 2 or more pain locations. Radicular pain and muscle pain were the most common types of pain in the GBS patients during the acute phase. Pain in GBS may be attributed to several possible causes. First, inflamed or damaged large myelinated sensory fibers may lead to dyesthesias and muscle pain in the extremities, which may account for the lower limbs being the most frequently reported pain location. Second, inflammatory reactions may occur. The affected nerve roots may lead to radicular nociceptive nerve pain that affects the lower back or back with radiation to the extremities or trunk. Third, small nerve fibers can also be affected in GBS. Pan et al. studied the intraepidermal nerve fiber density in 20 patients with GBS and found that 55% of the patients showed a reduced intraepidermal nerve fiber density with morphological evidence of nerve degeneration. Martinez et al. used quantitative sensory testing and determined that GBS patients with neuropathic pain had more abnormalities in cold and heat detection thresholds. The small-fiber sensory impairments during the acute stage were correlated with paresthesia. Finally, different immune antibodies may be mediated by different neural regions and tissue damage; thus, there are multiple pain types and locations in GBS patients during the acute phase.
the acute phase. Further studies are needed to confirm our hypotheses.

There are several limitations of our study. It was a cross-sectional study, and we could not assess the dynamic changes in pain and disability in the GBS patients. As we only included patients in the acute stage, the correlation between pain and the long-term outcomes of the GBS patients could not be evaluated. However, many clinicians and patients with GBS did not pay attention to pain symptoms, and the treatment of pain symptoms were lack. Thus, we could not evaluate the treatment outcomes for the pain symptoms. The lack of data on the mood of the patients with GBS was also a limitation because patients suffering from anxiety and depression could also complain of more pain, which might affect the incidence of pain in GBS patients.

Author contributions

Conceptualization: Shaoli Yao, Hongyu Zhou.
Data curation: Shaoli Yao, Hongxi Chen, Ziyan Shi.
Formal analysis: Ju Liu, Zhiyun Lian, Weihong Ge, Hongyu Zhou.
Investigation: Ju Liu, Zhiyun Lian, Weihong Ge, Hongyu Zhou.
Methodology: Shaoli Yao, Hongyu Zhou.
Resources: Shaoli Yao, Qin Zhang, Huiru Feng, Qin Du, Jinlu Xie.
Software: Hongxi Chen.
Writing – original draft: Shaoli Yao.
Writing – review & editing: Hongyu Zhou.

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