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Pain during the acute phase of Guillain–Barré syndrome

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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 (55%–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.[8,9] 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,[17] MS,[12,18] 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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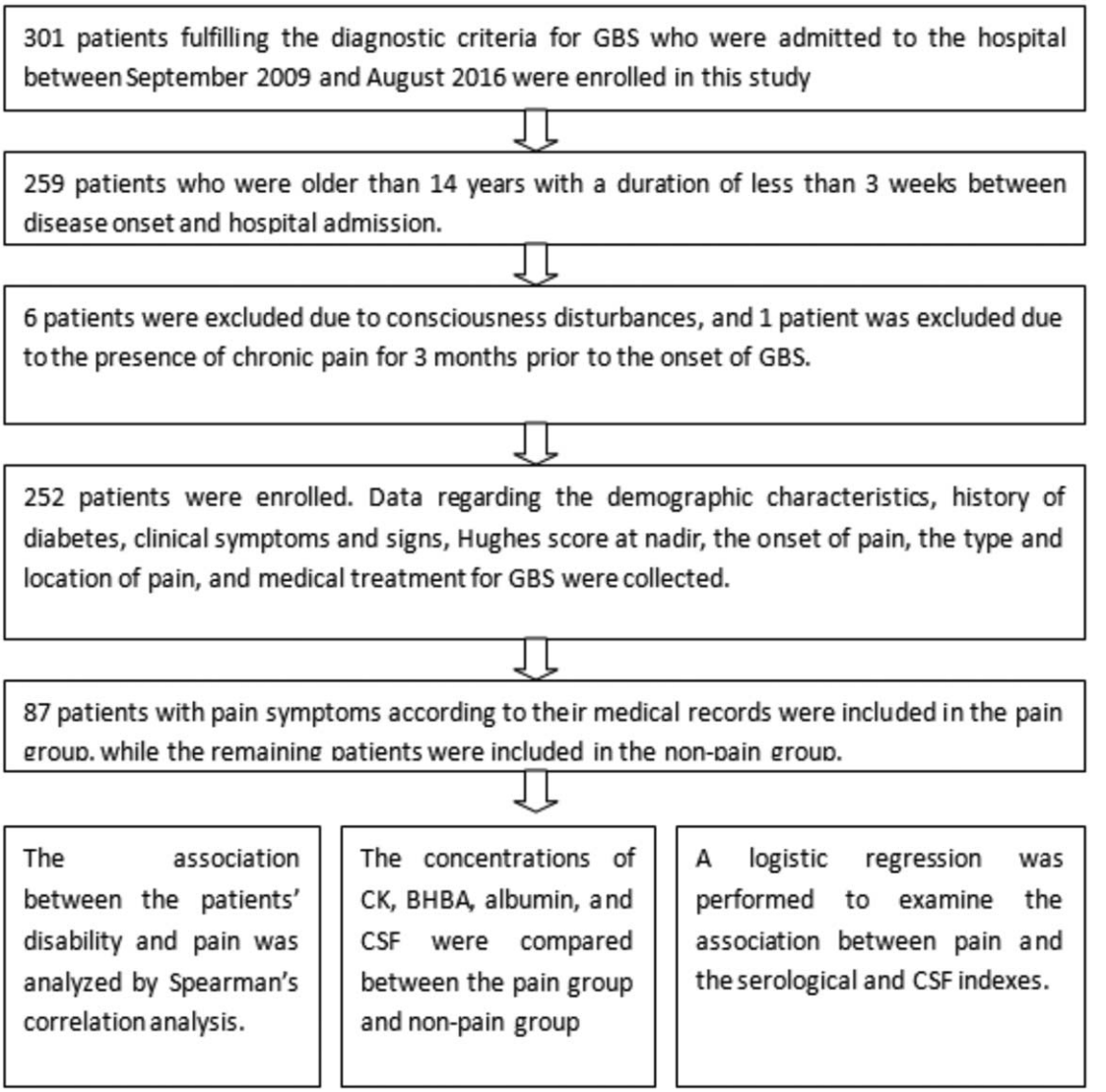

Figure 1. Flowchart of the subject enrollment. This study was based on a database comprising 301 consecutive GBS patients. Following the established inclusion and exclusion criteria252 GBS patients were enrolled in the study.

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 difficult; 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 time of pain onset, the type and location of pain, and the medical treatment for GBS were collected from the medical records of the enrolled patients. The pain group consisted of GBS patients with medical records indicating pain symptoms. 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 basic demographic and clinical characteristics of the 252 GBS patients are summarized in Table 1. The pain characteristics of the 87 GBS patients who reported pain are summarized in Table 2.

The Hughes functional grading scale was used to evaluate the severity of the patients' disabilities.[21] 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 score 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.[22] 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

Table 1

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

	Values
Baseline	
Male, n (%)	143 (56.7)
Age (mean ± SD)	50.27 ± 18.06
GBS categories	
AIDP	233 (92.5)
MFS	8 (3.2)
AMAN	8 (3.2)
Others	3 (1.1)
Acute phase, n (%)	
Symptoms and signs	
Cranial nerve involvement	159 (63.1)
Ataxia	49 (19.4)
Pain	87 (34.5)
Sensory disturbances*	97 (38.5)
Severely affected†	171 (67.9)
Autonomic functions	
Tachycardia	23 (9.1)
Hypertension (n = 226)‡	40 (17.7)
Gastrointestinal dysfunction	23 (9.1)
Bladder dysfunction	24 (9.5)
Postural hypotension	8 (3.2)
GBS medical treatment	
IVIg only	178 (70.6)
IVIg+methylprednisolone	13 (5.2)
None	47 (18.6)

AIDP = acute inflammatory demyelinating polyneuropathy, AMAN = acute motor axonal neuropathy, GBS = Guillain–Barré syndrome, MFS = Miller–Fisher syndrome, IVIg = IV immunoglobulin, Ig = immunoglobulin.

* Sensory disturbances = abnormal vibration sense/pinprick.

† Severely affected = unable to walk unaided = HFGS at nadir ≥ 3.

‡ Given percentages are based on the number of patients without a history of hypertension.

Table 2

Pain characteristics of 87 patients in the acute phase.

	Values
Baseline	
Male, n (%)	53 (60.9)
Age (mean ± SD)	(48.29 ± 16.96)
GBS categories, n (%)	
AIDP	85 (97.7)
AMAN	1 (1.15)
MFS	1 (1.15)
Location of pain, n (%)	
Lower limbs	51 (58.6)
Lower back or back	26 (29.9)
Headache	18 (20.7)
Neck	15 (17.2)
Interscapular	17 (19.5)
Extremities	19 (21.8)
Visceral*	7 (8.0)
Two or more pain locations, n (%)	40 (46.0)
Interpretation of pain†, n (%)	
Radicular pain	26 (29.9)
Meningism	13 (14.9)
Painful paresthesia/dysesthesia	17 (19.5)
Muscle pain	26 (29.9)
Unknown	5 (5.8)
Pain onset time, n (%)	
In the 2 weeks preceding weakness	29 (33.3)
Beyond 2 weeks preceding weakness	4 (4.6)
In the 2 weeks with weakness	53 (61.0)
More than 2 weeks with weakness	1 (1.1)
Severely affected‡, n (%)	57 (65.5)
Ataxia, n (%)	23 (26.4)
Cranial nerve involvement, n (%)	42 (48.3)
None	47 (18.6)

AIDP = acute inflammatory demyelinating polyneuropathy, AMAN = acute motor axonal neuropathy, GBS = Guillain–Barré syndrome, MFS = Miller–Fisher syndrome.

* Visceral pain refers to abdominal pain that could not be localized.

† The interpretation of pain is based on the case description.

‡ Severely affected = unable to walk unaided = HFGS at nadir ≥ 3.

(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.

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 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 (29.9%) 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 ($r = -0.152$, $P = .016$). 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.

Table 3

Correlation between the disease severity and pain.

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.

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 ($\beta = 0.424$, $P = .024$).

4. Discussion

Previously, the pain component of GBS has hardly got much attention. In 1984, Ropper and Shahani were the first to publish an article regarding pain in GBS.[23] These authors found that the incidence of pain in GBS patients ranged from 55% to 89%.[4,7,8] In our study, 34.5% of the patients reported pain during the acute phase of GBS. Multiple reasons may contribute to the lower incidence of pain observed in our study. Firstly, we only included patients within the first 3 weeks of GBS onset, thus, there may have been a loss of some of patients. Secondly, patients did not reported their pain even though it was present (a frequent occurrence when patients did not want to divert the physicians attention from treating the primary disease). Third, the pain assessment methods may be different (the pain might not been mentioned by the patient in describing their complaint), and the incidence of pain may differ among the subtypes of GBS. Finally, pain tolerance may differ among individuals with different ethnicities. In our study, 33.3% of the patients had experienced pain during the 2 weeks prior to the onset of weakness, and 61.0% of the patients had experienced pain during the 2 weeks after the onset of weakness, which is consistent with previous studies.[8]

Recently, the relationship between pain and disability in GBS patients has gradually gained attention but remains controversial. In a previous study, no significant correlation was observed between disability and pain intensity.[4] However, pain intensity 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.[8] 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 has 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.[4] 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 dysesthesia and muscle pain in the extremities,[8] 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.[24] Third, small nerve fibers can also be affected in GBS. Pan et al[25] 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[26] 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

Table 4

Comparison of the serological indexes and CSFP concentrations between the pain and nonpain groups.

	P	*P*[1]
Serological indexes		
UA*	.8505	.695
Albumin*	.1693	.256
CSFP concentration†	.0074	–

CSFP = cerebrospinal fluid protein, *P*[1] = adjusted for age and gender, UA = uric acid.
* Based on a Student's *t*-test.
† Based on a rank sum test.

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.

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

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References

[1] Ye Y, Zhu D, Wang K, et al. Clinical and electrophysiological features of the 2007 Guillain–Barré syndrome epidemic in northeast China. Muscle Nerve 2010;42:311–4.
[2] Peña L, Moreno C, Gutierrez-Alvarez A. Pain management in Guillain–Barre syndrome: a systematic review. Neurologia 2015;30:433–8.
[3] Liu J, Wang L, McNicol E. Pharmacological treatment for pain in Guillain–Barré syndrome. Cochrane Database Syst Rev 2013; CD009950.
[4] Moulin D, Hagen N, Feasby T, et al. Pain in Guillain–Barré syndrome. Neurology 1997;48:328–31.
[5] Bernsen R, Jager A, Schmitz P, et al. Long-term sensory deficit after Guillain–Barré syndrome. J Neurol 2001;248:483–6.
[6] Forsberg A, Press R, Einarsson U, et al. Impairment in Guillain–Barré syndrome during the first 2 years after onset: a prospective study. J Neurol Sci 2004;227:131–8.
[7] Ruts L, van Koningsveld R, Jacobs B, et al. Determination of pain and response to methylprednisolone in Guillain–Barré syndrome. J Neurol 2007;254:1318–22.
[8] Ruts L, Drenthen J, Jongen J, et al. Pain in Guillain–Barre syndrome: a long-term follow-up study. Neurology 2010;75:1439–47.
[9] Rekand T, Gramstad A, Vedeler C. Fatigue, pain and muscle weakness are frequent after Guillain–Barré syndrome and poliomyelitis. J Neurol 2009;256:349–54.
[10] Brambilla D, Mancuso C, Scuderi MR, et al. The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. Nutr J 2008;7:29.
[11] Hooper DC, Scott GS, Zborek A, et al. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. FASEB J 2000;14:691–8.
[12] Bagasra O, Michaels FH, Zheng YM, et al. Activation of the inducible form of nitric oxide synthase in the brains of patients with multiple sclerosis. Proc Natl Acad Sci U S A 1995;92:12041–5.
[13] Kean RB, Spitsin SV, Mikheeva T, et al. The peroxynitrite scavenger uric acid prevents inflammatory cell invasion into the central nervous system in experimental allergic encephalomyelitis through maintenance of blood-central nervous system barrier integrity. J Immunol 2000;165: 6511–8.
[14] Davies KJ, Sevanian A, Muakkassah-Kelly SF, et al. Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. Biochem J 1986;235:747–54.
[15] Ames BN, Cathcart R, Schwiers E, et al. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78: 6858–62.
[16] Roche M, Rondeau P, Singh NR, et al. The antioxidant properties of serum albumin. FEBS Lett 2008;582:1783–7.
[17] Peng F, Yang Y, Liu J, et al. Low antioxidant status of serum uric acid, bilirubin and albumin in patients with neuromyelitis optica. Eur J Neurol 2012;19:277–83.
[18] Peng F, Zhang B, Zhong X, et al. Serum uric acid levels of patients with multiple sclerosis and other neurological diseases. Mult Scler 2008;14: 188–96.
[19] Su Z, Chen Z, Xiang Y, et al. Low serum levels of uric acid and albumin in patients with Guillain–Barre syndrome. Medicine (Baltimore) 2017;96:e6618.
[20] Asbury A, Cornblath D. Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 1990;27(suppl):S21–4.
[21] Hughes R, Newsom-Davis J, Perkin G, et al. Controlled trial prednisolone in acute polyneuropathy. Lancet 1978;2:750–3.
[22] Fokke C, van den Berg B, Drenthen J, et al. Diagnosis of Guillain–Barré syndrome and validation of Brighton criteria. Brain 2014;137(Pt 1): 33–43.
[23] Ropper A, Shahani B. Pain in Guillain–Barré syndrome. Arch Neurol 1984;41:511–4.
[24] Gorson K, Ropper A, Muriello M, et al. Prospective evaluation of MRI lumbosacral nerve root enhancement in acute Guillain–Barré syndrome. Neurology 1996;47:813–7.
[25] Pan C, Tseng T, Lin Y, et al. Cutaneous innervation in Guillain–Barré syndrome: pathology and clinical correlations. Brain 2003;126(pt 2):386–97.
[26] Martinez V, Fletcher D, Martin F, et al. Small fibre impairment predicts neuropathic pain in Guillain–Barré syndrome. Pain 2010;151:53–60.