Thirugnanam Umapathi11 and Nobuhiro Yuki2
1Department of Neurology, National Neuroscience Institute, Singapore
2Departments of Microbiology and Medicine, National University of Singapore, Singapore
1Author for correspondence:
Tel.: +65 635 771 71
Fax: +65 635 771 37
umapathi@nni.com.sg

Pain in Guillain–Barré syndrome


Pain has been recognized as an important symptom of Guillain–Barré syndrome (GBS). The article under review prospectively studied the phenomenon of pain in a cohort of 156 GBS patients for a period of 1 year. It confirmed that pain of significant intensity is relatively common in all subtypes of GBS. It may start before the onset of other symptoms. It correlates with sensory loss, severity of the GBS at its nadir and the presence of diarrhea. In the recovery/chronic stages it correlates with weakness, disability and fatigue. Up to a third of patients have pain at 1 year.

KEYWORDS: Guillain–Barré syndrome • pain • peripheral neuropathy

Guillain–Barré syndrome (GBS) is the most common acute postinfectious polyneuropathy [1]. It is usually triggered by a dysimmune response to an infection, such as Campylobacter jejuni. Weakness and numbness develop acutely, and reach a nadir in 2–3 weeks. Most patients recover, although approximately 10% have an adverse outcome, including death. The main cause of morbidity is respiratory and bulbar muscle weakness. Three main subtypes of GBS are recognized – acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy and Miller Fisher syndrome (MFS).

Pain in GBS has generally been under-recognized. Clinicians often focus on progressive weakness and life-threatening complications of GBS, such as bulbar and respiratory paralysis. Underreporting is also likely, as the abovementioned sequelae of GBS impede the patients’ ability to express the presence and severity of pain.

The initial description of GBS by Guillain et al. did describe pain [2]. In 1984, Ropper and Shahani published a seminal article on pain in GBS [3]. A total of 29 patients were prospectively studied for the occurrence of pain, 16 had muscular pain early in the illness and in four it preceded the onset of weakness. Pain was located in the thighs and lower back. There was no association with specific clinical signs, electrophysiological abnormalities or pathological evidence of inflammation in the dorsal root ganglia.

Subsequent reports have further characterized the pain that occurs in GBS [4–11] and its subtypes [12–14]. Moulin et al. studied 55 consecutive GBS patients for 24 weeks [9]. A total of 89% reported pain, with 47% grading it as severe. Pain was described as deep aches in the lower back and legs. The patients also had dysesthesia in the extremities. The former improved with time, but the latter remained in a small group of patients.

Another study suggested that the pain may last up to 2 years in some patients [5]. Likewise, Bernsen et al. reported muscle aches and cramps in 48% of a cohort of GBS patients 3–6 years after GBS [15]. These symptoms were associated with the presence of objective sensory deficits.

Rutts et al. studied pain in 223 GBS patients for up to 52 weeks [10]. In total, 55% of GBS patients had pain, 70% of whom already had it before the onset of weakness. In addition to back pain and dysesthesia, the authors also described radicular pain in some patients. As in the previous studies, a subset of patients developed chronic pain lasting for as long as 6 months. Intravenous methylprednisolonolone had no effect on pain. The Dutch GBS study group has extended this in the GBS Research About Pain and Heterogeneity (GRAPH) study to better document the long-term clinical course of pain in GBS [16].

Methods & results
GRAPH is a prospective 1-year study of pain in 170 GBS patients, aged 12 years and above [16]. Patients with related conditions, namely Bickerstaff encephalitis and acute-onset chronic inflammatory demyelinating polyneuropathy, were excluded. Patients who were
Key Paper Evaluation

too ill and with an expected survival of less than 1 year were also not included. GBS patients were subclassified into GBS and MFS according to standard criteria [17,18], but the pure motor variant was simply defined as GBS without pinprick and vibration sensory deficits. Based on standard electrodiagnostic studies, nerves were subclassified as demyelinating, axonal, inexcitable, equivocal or normal [19].

The attending neurologist filled a standard questionnaire at weekly intervals and at 6 months after onset of illness. The patients filled additional questionnaires at 3, 6, 9 and 12 months after inclusion. The investigators monitored compliance closely. The questionnaires enquired in detail about the presence and quality of pain in the past week. These aspects of pain were specifically delved into:

- Presence of chronic pain 3 months before the onset of GBS, so as to differentiate this from that experienced after the onset of GBS;
- Pain in the 2 weeks before and since the onset of weakness;
- Location of pain;
- The use of various analgesics.

In addition, the following information was collected:

- Neurological symptoms, signs and clinical signs of autonomic dysfunction;
- Treatment and disease course;
- Neurological impairment, using Medical Research Council (MRC) sum score [23], and a modified Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score [24,25];
- Disability, using GBS disability score [26], Overall Disability Sum Score (ODSS) [25,27] and fatigue disability score [28];
- Antiganglioside antibodies [29–32] and type of preceding infections [33] were tested for.

The first 3 weeks, when all patients had reached the nadir of weakness, was deemed the acute phase. Longitudinal analysis of pain intensity scores was performed using repeated-measurement analysis of variance. The cohort was divided into subgroups based on age, gender, GBS subtypes, neurological deficits, disability, treatment received, electrophysiological subtypes and antecedent infections.

Results

Out of the 170 patients initially enrolled, 156 satisfied all inclusion and exclusion criteria. In total, 138 had GBS, while 18 had MFS and 83% of the GBS patients and 67% of the MFS were deemed to have severe illness, as they could not walk independently. In the whole cohort, a significant number of individuals, 22%, were already chronic pain sufferers, mainly in the joints and back. Half of these patients were taking daily analgesics.

In the acute phase, 66% of patients reported pain, slightly lower than the 89% reported by Moulin et al. [9]. It was more common in the GBS group (including the pure motor variant) compared with MFS: 69% GBS and 44% of MFS (p < 0.05). This difference was not present in the chronic phase – that is, after 3 weeks. A total of 36% of patients already had pain at a median time of 5 days before the onset of weakness. This was again more common in the GBS than the MFS group (40 vs 6%; p < 0.01).

Patients with sensory disturbances were more likely to have pain compared with those with pure motor deficits. The majority, 86%, described the pain as moderate-to-severe despite analgesics. The pain was located at the extremities and the back. Often it was reported in more than one location and appeared to follow the distribution of weakness. In MFS, neck pain and headache were common.

In the chronic phase, pain was more common in those who already had pain in the acute phase. They also experienced more intense pain. In the first 6 months, pain prevalence was similar in the patients with mild and severe GBS. Thereafter, patients who had severe GBS were more likely to have pain. At 1 year, 38% continued to have pain. The presence of pre-existent chronic pain did not influence the occurrence of pain at any stage after GBS.

At all stages, pain intensity was worse among GBS (non-MFS) patients, females and patients with sensory abnormalities, prior diarrhea and in the more severely affected patients. Greater impairment, disability and fatigue correlated with pain intensity in the chronic, but not acute, phase. There was no correlation with age, treatment with methylprednisolone, antiganglioside antibodies and electrophysiological subtype of GBS (i.e., demyelinating or axonal) and upper respiratory antecedent infections. Depression, anxiety and quality of life indices were not assessed.

Discussion & significance

The main points of this article are:

- Pain is relatively common in all subtypes of GBS;
- Pain is of significant magnitude;
- Pain starts a few days before the onset of weakness;
- Pain correlates with sensory loss, severity of the disease at its nadir and the presence of diarrhea;
- In the recovery/chronic stages, pain correlates with weakness, disability and fatigue;
- Up to a third of patients have pain at 1 year; those who suffered a more severe form of GBS and those who had pain in the acute stage are more likely to have chronic pain;
• There are two broad types of pain in GBS. The first starts before the onset of weakness and until hospital discharge and is mainly radicular, muscle pain and dysesthesia of the extremities. The second is observed during the chronic stage when patients are undergoing rehabilitation. Then the patients complain of dysesthesia, muscle pain and arthralgia in the limbs; and these are associated with weakness and disability.

The article raises a few interesting possible causes for pain in GBS.

First, neuropathic pain, where inflammed or damaged large myelinated sensory fibers may lead to the dysesthesia, as well as the muscle pain in the extremities. This may explain the correlation of pain with severity of illness at nadir in the acute phase. Animal studies have suggested a role for T-cell mediated inflammation and the release of proinflammatory cytokines producing thermal hyperalgesia and allodynia in experimental autoimmune neuritis [32,33]. 

Hence the lack of efficacy of additional anti-inflammatory treatment with methylprednisolone is surprising.

Second, small sensory and autonomic fiber (unmyelinated C and thinly myelinated A-d) pathology may be related to pain in GBS. Pan et al. studied the intraepidermal nerve fiber density (IENFD) of 20 patients with GBS [34]. They demonstrated that 55% had reduced IENFD, with morphological evidence of nerve degeneration. IENFD was related to dysautonomia, but there was no difference in IENFD between those with and without neuropathic pain. Matinez et al. addressed this same issue using quantitative sensory testing [35]. GBS patients with neuropathic pain had more abnormalities in cold and heat detection thresholds and to suprathreshold heat stimuli. Small-fiber sensory impairment at the acute stage was correlated with the intensity of burning pain and predicted residual neuropathic pain.

Nerve root inflammation may underlie radicular pain; however, in this study back pain was more common than radicular pain, suggesting that muscle ache and arthralgia, possibly related to immobilization, may be more important. Ropper et al. also did not find a correlation between the pathologic evidence of inflammation in dorsal root ganglia and pain [3]. They found that the serum creatine kinase level was elevated in ten out of 13 patients with pain and only one of eight without pain, suggesting that alterations in muscle related to neurogenic changes may cause the typical pain of GBS. This may also explain the correlation of pain with disability in the chronic stages.

The possibility of superimposed compression palsies developing in disabled patients and contributing to neuropathic pain in the limbs was not addressed by the authors.

The weaknesses of this study will now be discussed. First, only patients aged 12 years and above were considered. This was unfortunate because previous studies have suggested that pain may be a bigger problem in children with GBS. Korinthenberg et al. studied 53 boys and 42 girls with a median age of 6.2 years old [8]. The first symptom was usually a disturbance of gait or neuropathic pain. At the nadir of illness, 79% complained of neuropathic pain, half of whom reported it as severe. Pain as a primary complaint, preceding muscular weakness and areflexia, was also reported in a series of pediatric GBS patients by Monteiro et al. [36].

Second, symptoms closely associated with pain and disability, such as depression and anxiety, as well as quality of life indices, were not assessed. This is important on its own merit to fully appreciate the impact of pain in GBS patients. In addition, depression, anxiety and poor quality of life may confound the observation by increasing the prevalence and intensity of reported pain. Previous studies revealed conflicting evidence. One did not find significant correlation between disability and pain intensity [9], while another demonstrated an interaction between fatigue, pain and weakness in recovered GBS patients [37].

Expert commentary & five-year view

So how does this article influence our current and future practice?

• Clinicians should look for pain in all patients. Treat it aggressively; and because it appears to be both muscular, as well as neuropathic, in nature, different types of analgesics may have to be used for adequate symptom control;

• Mobilization of limbs and attempts to reduce disability may be important to control pain in the latter recovering stages;

• Intravenous immunoglobulin, by reducing disease severity, improving recovery time and minimizing chronic disability, is an important aspect of managing the pain of GBS. Future studies should look at whether severe pain in the acute stage of mild GBS should be an indication for intravenous immunoglobulin;

• Diarrheal illnesses appear to be an important cause of GBS in many parts of the world. Diarrhea is associated with poorer prognosis as far as outcomes of GBS are concerned [38]. This article has demonstrated that it is also associated with pain, and adds to the impetus for better public health measures to control diarrheal illness, in particular, C. jejuni enteritis;

• The authors have alluded to small-fiber dysfunction in GBS. Similar to in the study by Pan et al. [34], examination of small sensory and autonomic fibers in the skin may help to better understand the phenomenon of pain in GBS. Recently the technique of studying dermal and epidermal unmyelinated, as well as myelinated nerve fibers, has been used to understand the pathophysiology of a number of diseases, including Charcot–Marie–Tooth disease [39,40], chronic inflammatory demyelinating polyneuropathy [41] and diabetic neuropathy [42,43]. We predict that these methods will be used in more GBS research in the next 5 years.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Papers of special note have been highlighted as:

• of interest

• Comprehensive review of Guillain–Barré syndrome (GBS).

• Original description of GBS.

• Seminal article, stressing the importance of recognizing pain in GBS.


• Highlights pain as an important presenting feature of GBS in children.


• Demonstrated a lack of benefit of additional corticosteroids in controlling pain in GBS.


• Pain is also present in the less common variants of GBS.

• Pain is also present in the pure motor forms of GBS.


• Landmark study demonstrating small-fiber pathology in GBS.


• Study of pain in pediatric GBS.


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