A Nationwide Survey of Spinal Cord-Related Pain Syndrome in Japan: Clinical Characteristics and Treatment

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Abstract:

Introduction: In this study, we defined chronic neuropathic pain (NeP) in patients with diseases associated with spinal cord damage, such as spinal cord-related pain syndrome, and performed a nationwide survey investigating the prevalence, actual status, and features of this syndrome in Japan in order to gather basic information needed for planning control measures.

Methods: In this nationwide epidemiologic survey, a mail-in questionnaire was sent to 3,206 institutions throughout Japan certified by the Japanese Orthopaedic Association (2,065 institutions) and the Japan Neurosurgical Society (1,141 institutions). The survey included the number of patients, frequency, and type of allodynia, concomitant diseases, and types of and responses to treatment.

Results: Valid responses were obtained from 552 institutions on 3,401 patients. Of these, 1,719 (50.5%) patients experienced no pain, and thus the study involved the analysis of data of the remaining 1,682 patients with pain. The most frequent underlying conditions were cervical spondylotic myelopathy (26.7%), spinal cord injury (17.4%), and ossification of the posterior longitudinal ligament (OPLL) of the cervical spine (14.1%). Among the 1,682 patients, 62.5% reported at-level pain, among which 43.0% presented with allodynia. On the other hand, 38.7% presented with below-level pain. The majority of patients (73.4%) used nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants (46.6%). The effectiveness of treatment was significantly higher in patients using anticonvulsants (31.1%) than in those using other medications. About a third of the patients stopped the treatment for either lack of effect or adverse effects.

Conclusions: The characteristics of NeP in patients with spinal cord-related pain syndrome varied according to its level in relation to the affected spinal segment (at-level and/or below-level). Unfortunately, medications are sometimes ineffective and have potential adverse effects. Further classification of allodynia is needed for effective symptom-based treatment.

Keywords:

spinal cord-related pain syndrome, nationwide survey, neuropathic pain, clinical characteristics, treatment

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Introduction

Neuropathic pain (NeP), as defined by the International Association for the Study of Pain (IASP), is pain initiated or caused by a primary lesion or dysfunction in the nervous system[1)]. NeP may be spontaneous or evoked, as an increased response to a painful stimulus (hyperalgesia) or a painful response to a normally nonpainful stimulus (allodynia)[2)]. Many common diseases and interventions that produce lesions in the somatosensory pathways in the peripheral or central nervous system can cause NeP[3)]. For example, a prevalence rate of NeP of 19% has been reported in systematic reviews of patients with cancer, with similar estimates (20%) among patients with type 2 diabetes[4-7)]. In one cross-sectional study of patients with spinal disorders, a high frequency of chronic NeP was found in patients with dis-

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Table 1. Criteria of Spinal Cord-related Pain Syndrome.

Pain Characteristics at Region 1. Persistent pain and/or numbness (three months or more) at and/or below the level of the affected spinal cord segment identified by magnetic resonance imaging inspection.
Pain Characteristics at Region 2. Sensory disturbances at the pain regions or those around.
Imaging Findings. Compressive lesions, signal intensity areas, intumescences, or spinal cord atrophy consistent with neurological findings.
Characterization of Pain as an Intractable Disorder. Poor effect of NSAIDs on pain.
Exclusions. Pain associated with neurodegenerative diseases, brain diseases, and peripheral nerve disorders (e.g., diabetic neuropathy, strangulated neuropathy).

Table 2. Grade Classification of Spinal Cord-related Pain Syndrome.

Grade 0: No pain, numbness, and/or hyper- or hypoesthesia
Grade 1: No debilitating pain
Grade 2: Inability to work because of pain
Grade 3: Pain interferes with daily life activities
Grade 4: Pain interferes with living alone

eases associated with spinal cord damage[8].

Spinal-cord-associated diseases, such as spinal myelopathies, ossification of the posterior longitudinal ligament (OPLL), syringomyelia, and spinal cord injury, can cause chronic NeP, herein called spinal cord-related pain syndrome. Effective treatment of spinal cord-related pain syndrome can be difficult even if the symptoms are similar, and its pain is associated with a significant impairment in health-related quality of life along with a substantial economic burden[9-11]. Spinal cord-related pain syndrome should receive greater attention because it is the duty of any healthcare system to improve pain recognition and management.

Chronic NeP is a global burden. In a systematic review, van Hecke et al.[12] found that the worldwide prevalence of chronic NeP varied extensively, ranging from 1.3[13] to 17.9%[14]. Such variation is likely due not only to the disparate areas in which the investigations were conducted, but also to the different sociodemographic characteristics, methods of data collection, and definitions of chronic pain. Most studies define chronic pain as any persistent or intermittent pain that lasts more than three months, regardless of its intensity or frequency. Thus, these estimates of NeP include cases of mild and temporary pain. Breivik et al.[15] conducted a large-scale chronic pain survey on 15 European countries and Israel and reported a prevalence of chronic pain of 19%, in which chronic pain was defined as a "pain severity of ≥5 on a scale of 1-10, with a duration of ≥6 months, featuring pain at least twice a week within the past month."

There is even lack of basic information necessary to plan control measures against spinal cord-related pain syndrome, and this paucity is probably due to the small number of cases available through individual medical facilities. Therefore, we organized the "Spinal Cord-Related Pain Syndrome Research Group (through the Health and Labor Sciences Research Grants)" to conduct research on this topic. The objective of this nationwide survey was to determine the prevalence, actual status, and features of spinal cord-related pain syndrome in Japan and to gather sufficient data necessary for formulating control measures from the demographic characteristics of individuals and perspectives of clinical medicine and public health.

Materials and Methods

First, we defined the criteria of chronic NeP (greater than or equal to three months) in patients with diseases associated with spinal cord damage identified by magnetic resonance imaging inspection as "spinal cord-related pain syndrome." The criteria required an agreement between clinical findings (pain region and characteristics) and imaging findings (spinal cord damage consistent with neurological findings) (Table 1). Second, we also established a five-point grade classification to estimate the degree of pain (Table 2). In this nationwide epidemiologic survey, a mail-in questionnaire was used, which was sent to 3,206 medical facilities throughout Japan certified by the Japanese Orthopaedic Association (2,065 institutions) and the Japan Neurosurgical Society (1,141 institutions). Table 3 includes the questionnaire sent to these institutions. The questionnaire was designed to determine the number of patients in the past one year, as well as a detailed assessment of the frequency and type of allodynia, concomitant diseases, and types and effectiveness of treatment of these patients with grade ≥ 1 pain. The management of personal information and registration were performed by the staff at each institution based on their hospital records.

The χ^2 test was used to analyze the effects of each medication. A p-value less than 5% denoted the presence of statistical significance. The study protocol was approved by the Human Ethics Review Committee and Institutional Review Board of the corresponding author's affiliated institution.

Results

Grade classification of patients with spinal cord-related pain syndrome

Valid responses were obtained from 552 institutions (17.2%) with experience in treatment of patients with spinal cord-related pain syndrome. The responses included information on 3,401 patients. Patients were categorized using

Table 3. The Questionnaire Used in the Study (Translated from the Original Version in Japanese).

1. How many patients fulfilled the following criteria of spinal cord-related pain syndrome?
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4
The following questions are related to patients with ≥grade 1 pain (*see Table 2*).
2-1. How many patients presented with clinical symptoms at affected spinal cord segment levels (at pain level) ?
2-2. Of the above patients, how many presented with allodynia?
2-3. In how many patients did the following type of stimulus evoke pain? (Select all that apply)
Cold stimuli (e.g., metal)
Warm stimuli
Pressure
Pain relieved by covering
Spontaneous pain
3-1. How many patients presented with symptoms below the affected spinal cord segment (below pain level) ?
3-2. How many patients exhibited the following types of lower limb symptoms? (Select all that apply)
Sensation of muscle discomfort
Numbness and pain
Burning pain
Cold-induced pain
Allodynia
4. How many patients had the following concomitant diseases?
Cervical spondylotic myelopathy
Cervical disc herniation
Cervical spine OPLL
Cervical spondylotic radiculopathy
Syringomyelia
Thoracic spine OPLL
Thoracic spine OLF
Thoracic disc herniation
Spinal cord tumor
Spinal cord traumatic injury
Cervical sprain
Other
5. How many patients were provided with the following types of treatment for pain relief? (Select all that apply)
NSAIDs
Muscle relaxants
Anticonvulsants
Antidepressants
Anxiolytic agents
Herbal medicines
Physical therapy
Other medications

the above pain grade classification as follows: grade 0 (1,719, 50.5%), grade 1 (850, 24.1%), grade 2 (485, 14.3%), grade 3 (242, 7.1%), and grade 4 (105, 3.1%) (Fig. 1). We excluded the data of those with grade 0 because these patients experienced no pain (only numbness and/or hyper- or hypoesthesia) and the symptoms might be nonspecific for this syndrome; we analyzed only those of the remaining 1,682 (49.5%) patients with grade ≥ 1.

Characterization of symptoms in patients with spinal cord-related pain syndrome

Table 4 summarizes the clinical characteristics of the 1,682 patients. The most frequent diagnoses were cervical spondylotic myelopathy (n = 449, 26.7%), spinal cord injury (n = 292, 17.4%), and cervical spine OPLL (n = 238, 14.1%). Of the 1,682 patients, 1,051 (62.5%) reported pain at the affected level (at-level pain), among whom 452 (43.0%) presented with allodynia. The types of stimuli that

Table 3. continued

6-1. In how many patients were the medications effective? (Select all that apply)

	Very effective	Mildly effective	Poorly effective	Not effective
NSAIDs				
Muscle relaxants				
Anticonvulsants				
Antidepressants				
Anxiolytics				
Herbal medicines				

Very effective, symptoms disappeared; mildly effective, beneficial effects render the treatment an option for continuous therapy; poorly effective, very little effect—used as long-term medication due to lack of therapeutic options; not effective, drug discontinued despite lack of other therapeutic options.

6-2. How many patients had the following indications for treatment cessation?
Liver- and/or kidney-related side effects
Gastrointestinal side effects
Sleepiness, dullness
Dizziness, giddiness
Requested by patients (for reasons other than side effects)

NSAIDs, Nonsteroidal anti-inflammatory drugs; OPLL, ossification of posterior longitudinal ligament; OLF, ossification of ligament flavum

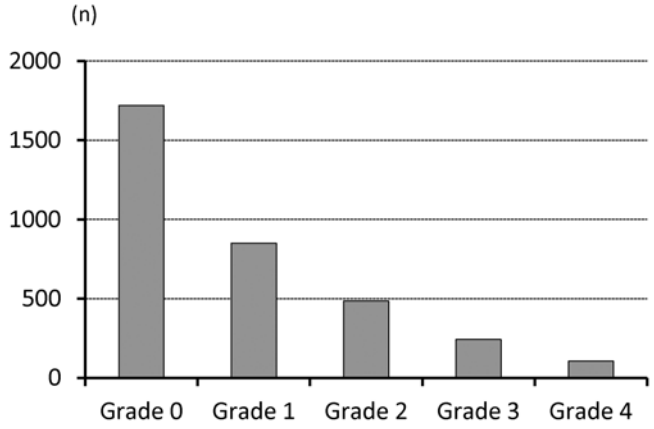

Figure 1. Classification of spinal-cord-related pain syndrome.

Table 4. Summary of the Data of the 1,682 Patients.

Disorders	
Cervical spondylotic myelopathy	449 (26.7%)
Spinal cord injury	292 (17.4%)
Cervical spine OPLL	238 (14.1%)
Cervical disc herniation	115 (6.8%)
Cervical spondylotic radiculopathy	92 (5.5%)
Spinal cord tumor	76 (4.5%)
Syringomyelia	61 (3.6%)
Thoracic spine OLF	48 (2.9%)
Cervical sprain	40 (2.4%)
Thoracic spine OPLL	33 (2.0%)
Thoracic disc herniation	18 (1.1%)
Others	77 (4.6%)
Characteristics of pain	
At affected level	1,051 (62.5%)
Allodynia	452 (43.0%)
Below affected level	651 (38.7%)

Data are shown as the number of cases (%). OPLL: ossification of the posterior longitudinal ligament; OLF: ossification of ligamentum flavum

evoked allodynia in these patients were spontaneous pain (n = 435, 96.2%), cold stimuli (n = 236, 52.2%), pressure (n = 215, 47.6%), covering (n = 180, 39.8%), and warm stimuli (n = 49, 10.8%) (Fig. 2). On the other hand, among the same patients, 651 (38.7%) presented with pain below the level of the affected area (below-level pain). In these patients, lower-limb symptoms included the following: numbness and pain (n = 440, 67.6%), sensation of muscle discomfort (n = 301, 46.2%), cold pain (n = 187, 28.7%), burning pain (n = 132, 20.3%), and allodynia (n = 114, 17.5%) (Fig. 3). Above-level pain was not assessed in this study.

Selection and effectiveness of medications for spinal cord-related pain syndrome

The majority of patients (n = 1,235, 73.4%) used nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants (n = 783, 46.6%). Some patients used anxiolytics (n = 492, 29.3%), anticonvulsants (n = 470, 27.9%), antidepressants (n = 414, 24.6%), or herbal medicines (n = 225, 13.4%) (Fig. 4). The effectiveness rates of these medications are shown in Fig. 5. The percentages of "very effective" and "mildly effective" were significantly higher in patients using anticonvulsants (31.1%) than in those using other medications (18.8% for antidepressants, 14.3% for NSAIDs, 12.4% for anxiolytics, 12.0% for herbal medicines, and 9.6% for muscle relaxants), as assessed by the χ^2 test. Among those patients, 546 (32.5%) stopped their medications. The most common reasons for withdrawal of medications were patient's own request (n = 160, 9.5%), sleepiness and/or dull-

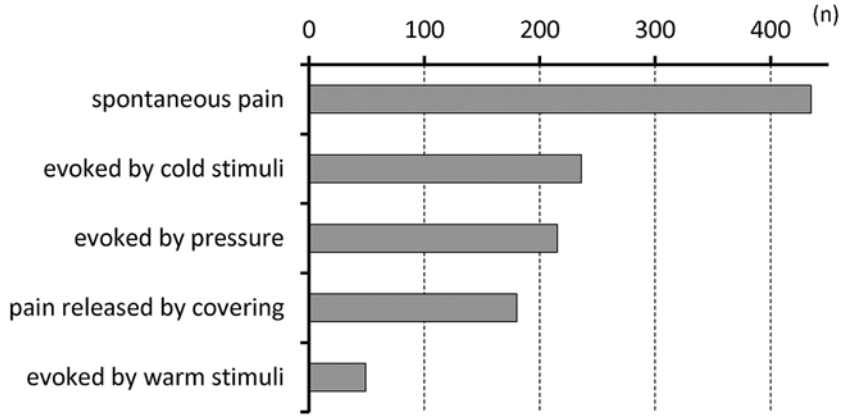

Figure 2. Types of allodynia in the patients at the affected level.

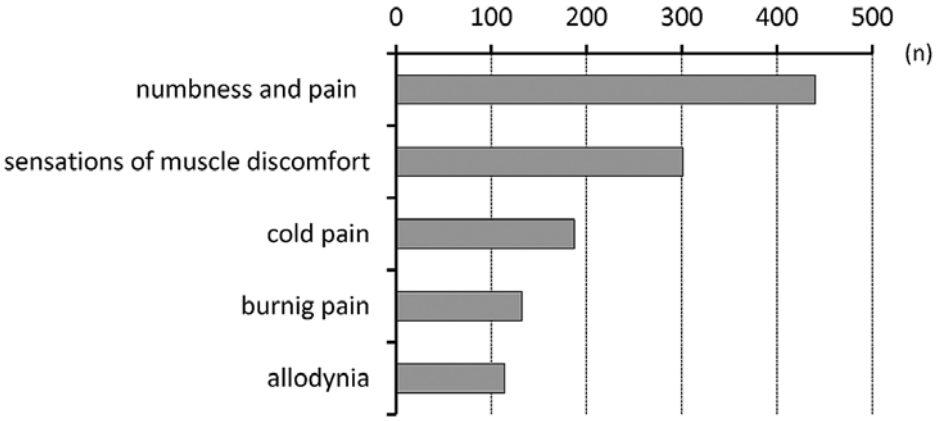

Figure 3. Types of lower-limb symptoms in patients with pain below the affected spinal level.

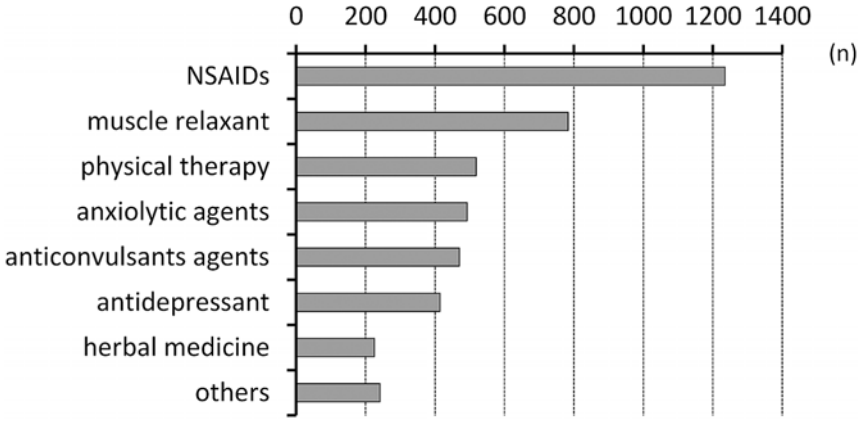

Figure 4. Types of medications used by patients with spinal-cord-related pain syndrome.

ness (n = 138, 8.2%), dizziness and/or giddiness (n = 134, 8.0%), gastrointestinal disorders (n = 96, 5.7%), and liver- and/or kidney-related side effects (n = 18, 1.1%) (Fig. 6).

Discussion

Previous studies on NeP arising from the spinal cord often included patients with spinal cord injuries, syringomyelia, and spinal intramedullary tumors[16-18]. Up to 80% of patients with spinal cord injuries develop chronic NeP, which can be localized below, at, or above the level of the spinal cord injury lesion[16]. The reported incidence of dysesthesia following the resection of intramedullary tumors is about 50%-70%[17]. These studies included small numbers of patients and provided only a few clinical details. In their cross-sectional study, Yamashita et al.[8] reported a prevalence of NeP related to spinal cord disorders of 53.3% (990/1,857). The frequency of NeP tended to be higher in pa-

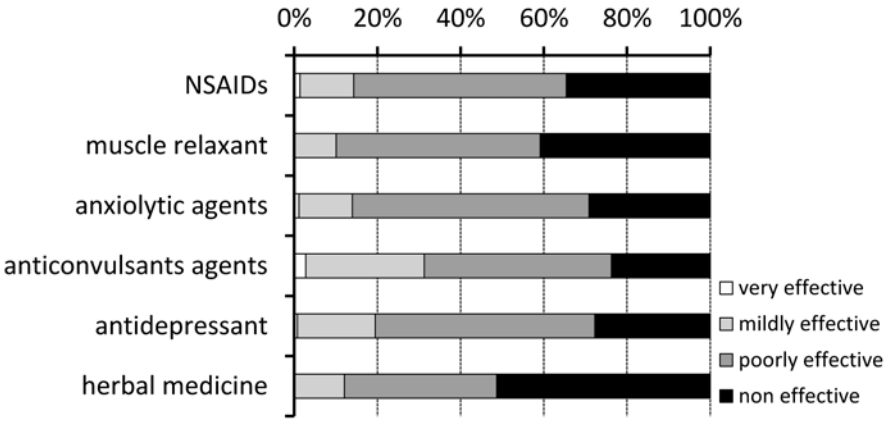

Figure 5. Effects of each medication type on patients with spinal-cord-related pain syndrome.

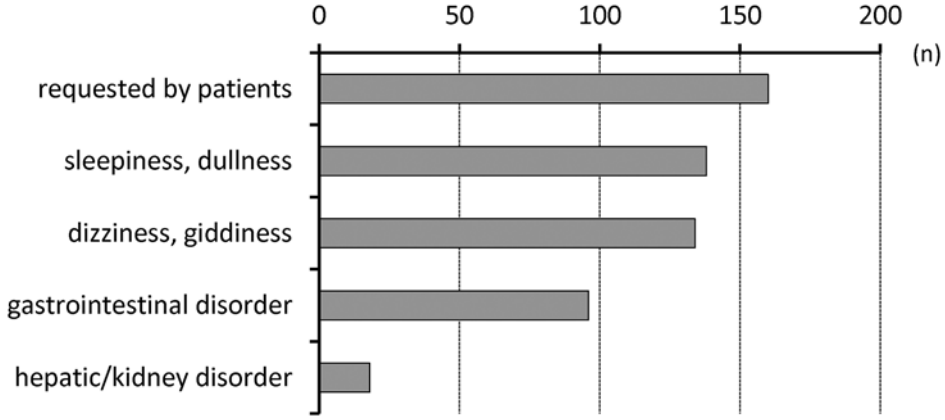

Figure 6. Reasons for withdrawal of medical treatment in patients with spinal-cord-related pain syndrome.

tients with diseases associated with spinal cord damage and lower in patients with diseases that primarily manifested as somatic pain. In this study, we termed chronic NeP in patients with diseases associated with spinal cord damage as "spinal cord-related pain syndrome." We conducted a nationwide survey on patients with this syndrome to assess the prevalence, actual status, and features of the syndrome in Japan, which were the basic information needed for planning control measures.

In our study, 49.5% (1,682/3,401) of patients meeting the criteria of spinal cord-related pain syndrome experienced pain. Among these patients, 62.5% (1,051/1,682) presented with at-level pain, whereas 38.7% (651/1,682) experienced below-level pain. Among patients with at-level pain, 43.0% (452/1,051) presented with allodynia. Furthermore, spontaneous pain (stimulus-independent) was more common than evoked pain (stimulus-dependent). On the other hand, in patients with below-level pain, only 17.5% (114/651) had allodynia: numbness and pain (67.6%) and sensations of muscle discomfort (46.2%) were the most common types of below-level pain. Our results indicated that the characteristics of NeP in patients with spinal cord-related pain syndrome also varied according to the location of pain in relation to the level of spinal column pathology.

The characteristics of NeP in patients with spinal cord injury are different in those presenting with at-level pain compared with patients with below-level pain. For at-level pain, 37%-50% of the patients seem to have damaged nerve root segments that could progressively induce sprouting, leading to the stimulation of primary afferent fibers and causing evoked persistent pain that is generally not related to activity or affected by position. On the other hand, in below-level pain, 76%-83% of the patients described pain as burning, tingling, numbness, aching, or throbbing[18,19]. In the majority of cases, NeP is associated with more than one pain mechanism, and the mechanism usually changes over time[20]. In addition, the same underlying pathology can cause different symptoms, whereas different diseases can sometimes present with similar symptoms.

Response to treatment is difficult and sometimes unpredictable[21-23]. Unfortunately, medications are sometimes ineffective in providing consistent significant pain relief for NeP and have the potential to induce adverse effects. In our study, although 73.4% of the patients used NSAIDs, only 14.3% described the treatment to be effective. In a previous study that provided a systematic review of the literature, it was concluded that there was no evidence supporting or refuting the benefits of oral NSAIDs in the treatment of NeP

related conditions[24]. Even anticonvulsants, the most effective medication in this study, which are considered the first-line treatment in the updated therapeutic algorithm for NeP by IASP[21], were found to be effective by only 31.1% in this survey. Interestingly, more than 30% of patients with spinal cord-related pain syndrome stopped their medications because they considered them to be ineffective or they thought they caused adverse effects. In addition to physical modulation, psychological factors also play an important role in the allodynic phenomena in patients with spinal cord-related pain syndrome[25]. Although pharmacological treatment is the mainstay of NeP treatment, the phenotype of NeP is reported to be associated with the efficacy of pharmacologic treatment, and symptom-based treatment can result in more efficient alleviation of NeP[20].

Further classification of allodynia according to the types of stimuli could provide additional information. This, together with the selection of a multidisciplinary approach, could enhance our understanding of the underlying mechanism(s) of pain in these patients and may help in the design of different management protocols. The low response rate to our survey, the selection of the study population, and the diagnosis accuracy of the patients with spinal cord-related syndrome recruited from multiple centers might have affected the accuracy of our prevalence estimations. Based on this perspective, we are planning a second survey on patients recruited from institutions with the largest number of patients in this survey, employing clinician- and patient-based measures to evaluate the nature of pain, daily life, quality of life, social loss, and effectiveness of treatment in patients with NeP grade ≥ 2[26].

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: Nakajima wrote and prepared the manuscript, and all of the authors participated in the study design. All authors have read, reviewed, and approved the article.

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