Prevalence of neuropathic pain in patients with rheumatoid arthritis

Te-Cheng Chung¹, Jeng-Hsien Yen¹², Tsan-Teng Ou¹², Hong-Wen Liu¹², Wen-Chan Tsai¹²

¹Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
²Kaohsiung Medical University, Kaohsiung, Taiwan

Objective: To study the prevalence of possible neuropathic pain in patients with rheumatoid arthritis (RA) in addition to investigating the correlation between disease duration and occurrence of neuropathic pain.

Methods: A questionnaire containing Brief Pain Inventory by Dr. Cleeland translated into Chinese was given to patients with RA in the rheumatologic outpatient department from March 2008 to June 2008 in a tertiary center in southern Taiwan. Objective sensory testing was also carried out with results recorded in the questionnaire. Latest level of serological markers for inflammation, erythrocyte sedimentation rate and C-reactive protein, of the patient were documented for investigation on possible correlation.

Results: One hundred patients fulfilling the 1987 revised criteria of the American College of Rheumatology for RA participated. Twenty-five patients were excluded due to insufficient background information for analysis. Of the seventy-five patients analyzed, female patients predominated (62 female, 84%), mean age was 55.64 years, average disease duration was 11.08 years, and 67/75 (89.33%) of the patients reported pain within one week prior to the clinic visit. Among the sixty-seven patients complaining of pain, they rated their worst pain intensity as 5.74 (range 1 to 10) on a numeric rating scale, with least pain intensity as 1.78 (range 0 to 9), and pain intensity most of the time as 3.54 (ranged 0 to 10). Among the 67 RA patients complaining of pain upon query, their average disease duration was 11.19 years; allodynia and altered pinprick threshold were found in 40 patients (59.70%) and 47 patients (70.15%), respectively.

Conclusion: Review of the literature states allodynia and altered pinprick threshold to be pathognomonic of neuropathic pain. 53 of the 67 patients (79.10%) complaining of pain showed positive for at least one objective sensory test. Nearly 80% of patients have neuropathic pain. Our study found that disease duration of RA does not correlate well with occurrence of allodynia or altered pinprick threshold. Patients with 2-year duration of RA may demonstrate a positive result for both allodynia and altered pinprick threshold; however, eight out of our seventy-five study subjects (10.1%) with over a 10-year disease duration (range 10-40 years) were negative for both.

Key words: Neuropathic pain, rheumatoid arthritis, allodynia, altered pinprick threshold

Introduction

Pain is a familiar complaint by patients seeking help from their physician. Patients complaining of different degree of pain are seen in daily rheumatologic practice. Chronic pain is defined as pain lasting longer than 3 to 6 months that may cause varying degree of physical dysfunction and trigger different psychological
conditions ranging from anxiety, depression, and personality changes that impaired the patient’s quality of life [1]. Clinically, the best known examples of neuropathic pain have been observed in patients with diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, phantom limb pain, nerve compression and entrapment neuropathy, post-stroke neuropathic pain, and multiple sclerosis...etc. Patients with rheumatoid arthritis (RA) experienced varying degrees of pain and different types of sensory deficit [1,2]. However, neuropathic pain in patients with RA is less reported in Taiwan, possibly due to lack of definite diagnostic criteria and standardized testing instruments for this complex condition. We started out to investigate the prevalence of possible neuropathic pain in patients with RA; correlation between disease duration of RA and occurrence of neuropathic pain were also studied.

The International Association for the Study of Pain (IASP) defines neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” [3]. Some have argued this definition has limited practical value for either clinical or epidemiological classification for the wide and diverse etiologies of neuropathic pain. Frequently, patients used terms as “tingling, burning, numbness...etc” instead of “pain” to describe what they experienced that disturbed their daily life activities. Physicians may raise suspicion of possible neuropathic pain if their patients demonstrated signs such as allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (a painful sensation of abnormal severity following a noxious stimulus and represents an exaggerated response to the same modality stimulus), hyperpathia (characterized by temporal abnormalities such as increased reaction to a stimulus and spatial abnormalities such as pain provoked in leg when arm is stimulated), autonomic dysfunction (skin color, temperature, sweating may be altered in involved area). Both allodynia and hyperalgesia are reported to be pathognomonic of neuropathic pain. Therefore, the presence of neuropathic pain can be inferred only, identifying possible neuropathic pain, instead of making a definite diagnosis [4]. Studies conducted in the United Kingdom and the U.S.A. have developed Douleur Neuropathique 4 (DN4) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), which includes a self-complete version, the S-LANSS, to identify patients with possible neuropathic pain. Nonetheless, validation (translation and back-translation) of the original (English) LANSS-scale has not yet been carried out in Chinese-speaking countries. Validated instrument available for pain evaluation in Taiwan originated from the work of Ger et al. in 1999 [5]. They conducted the validation of the Brief Pain Inventory (BPI) formulated by Cleeland et al. of the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care in 1983 [6]. Brief Pain Inventory has been validated into a dozen versions and languages; it is one of the most widely used instruments for pain evaluation. BPI applied a predominantly numeric rating scale (NRS) to evaluate the severity of pain, “0” as no pain and “10” as the worst pain imaginable; patients can pick a number in between to represent their pain intensity. Because pain is subjective, objective sensory testing via cotton wool brushing and pinprick threshold examination over tender areas contrasted to non-tender areas of the same patient was performed with results documented in our questionnaire containing validated BPI in Mandarin.

Methods

Initially, a questionnaire containing validated BPI by Ger LP et al. along with objective sensory testing on allodynia and altered pinprick threshold was devised; the questionnaire was sent to our Institutional Review Board for approval. The questionnaire was administered to patients of the rheumatologic outpatient department from March to July of 2008. One hundred patients fulfilling the 1987 revised criteria of the American College of Rheumatology for RA [7] signed informed consents and answered the questions along with the sensory test. Twenty-five patients were excluded due to insufficient background information for analysis.

Results

Of the seventy-five patients analyzed, female patients predominated (62 female, 84%), mean age 55.64 years (Fig. 1A), average disease duration 11.08 years (Fig. 1B), 67/75 (89.33%) patients stated they experienced pain within one week prior to the clinic visit. Among the sixty-seven patients complaining of pain, they rated their worst pain intensity as 5.74 (range 1 to 10) on the numeric rating scale, with least pain intensity as 1.78 (range 0 to 9), pain intensity most of the time as 3.54 (ranged 0 to 10), pain intensity upon query as 2.55 (ranged 0 to 10), occurrence of allodynia as 40 in 67 (59.70%), and occurrence of altered pinprick threshold as 47 in 67 (70.15%). 89.10% (53/67) of patients were positive for at least one objective sensory test.

Serum level of inflammatory markers C-reactive
Chung et al

Protein (CRP) and erythrocyte sedimentation rate (ESR) were available in 59 and 69 patients, respectively; average serum level of inflammatory markers were CRP 8.63 mg/L and ESR 30.74 mm/hour, respectively. Among the 67 RA patients complaining of pain upon query, their average serum level of inflammatory markers, if available, were CRP 9.46 mg/L (n = 51) and ESR 15.63 mm/hour (n = 61), respectively; their average disease duration was 11.19 years. Serum levels of inflammatory markers do not correlate with occurrence of allodynia and altered pinprick threshold (Fig. 2 and 3).

In the 8 patients who did not experience pain within one week prior to query, the occurrence of allodynia and altered pinprick threshold were 3/8 (37.5%) and 3/8 (37.5%), respectively. Their average disease duration was 10.125 years. Both allodynia and altered pinprick threshold were present in the three patients, their average disease duration, serum level of inflammatory markers were 3.67 years, CRP 0.89 mg/L (range 0.58-1.2 mg/L) and ESR 17.33 mm/hour (range 12-25 mm/hour), respectively.

Nearly 90% (67 out of seventy-five patients) of our

![Figure 1](image1.png)

**Figure 1.** Age distributions (1A) and distributions of disease duration (1B) among the patients with RA.

![Figure 2](image2.png)

**Figure 2.** The correlations between ESR and occurrence of altered pinprick threshold (2A) and allodynia (2B). Group 1: no pain in one week, Group 2: presence of pain in one week.

Abbreviations: ESR = erythrocyte sedimentation rate; APT = altered pinprick threshold.

![Figure 3](image3.png)

**Figure 3.** The correlations between CRP and occurrence of altered pinprick threshold (3A) and allodynia (3B). Group 1: no pain in one week, Group 2: presence of pain in one week.

Abbreviations: CRP = C-reactive protein; APT = altered pinprick threshold.
studied subjects complained of pain within one week prior to his or her clinic visit; among them, about 60% (n = 40) of patients demonstrated alldynia, and 70% (n = 47) showed altered pinprick threshold. 53 of the 67 patients (79.10%) complaining of pain demonstrated positive for at least one objective sensory test (cotton wool brushing or safety pinprick threshold). Assuming alldynia or altered pinprick threshold were sensitive and specific for neuropathic pain, about 80% of our patients complaining of pain may have possible neuropathic pain.

Our study found that disease duration of RA does not correlate well with occurrence of alldynia or altered pinprick threshold. Patients with 2-year duration of RA may demonstrate a positive result for both allodynia and altered pinprick threshold; however, eight out of our seventy-five study subjects (10.1%) with over 10-year disease duration (range 10-40 years) were negative for both.

Discussion

Rheumatologists see patients with pain in their everyday practice. With treatment, some patients achieved satisfactory pain relief and resumed their daily life activity; those less fortunate ones responded poorly to treatment and caused absence from, if not loss of, work for themselves and their families. The economic impact by patients with chronic pain is huge because they tend to work less and earn less [1]. Chronic pain such as diabetic neuropathy [8], post-herpetic neuralgia, phantom limb pain, and post-stroke neuropathic pain are conditions with neuropathic component and much complexity that renders neuropathic pain difficult to diagnose. Pathophysiologic mechanisms between nociceptive and neuropathic pain may overlap, therefore, many instruments for pain assessment have been developed [9]. Western countries have long realized the impact chronic pain can exert on public health, and many resources have been invested in studies on pain [10-13]. RA is the most common inflammatory arthritis afflicting 1% of the general population with greater female involvement, female/male ratio 2:1 to 4:1 [1]. It is not surprising to find female predominance in our study. Flare of RA may accompany local finding of inflammation (erythema, warmth, swelling, pain) along with elevation of inflammatory marker (CRP and ESR). However, it is not unusual to encounter patients with RA complaining of pain without clinical signs of inflammatory flare. Numbness and burning sensation were the most frequently complained of symptoms. Michael Bennett, editor of Neuropathic Pain by Oxford Pain Management Library, has stated that neuropathic pain can only be inferred instead of being objectively identified at present. A causal relationship between neuropathy and pain of the patient awaits to be established [4].

Neuropathic component may be suspected in patients with chronic pain that does not respond well to traditional remedies for nociceptive pain. Correct identification of neuropathic pain and appropriate medication may provide better relief of symptoms. We are interested in the prevalence of neuropathic pain among RA patients and the correlation between disease duration of RA and occurrence of neuropathic pain. 89.33% (n = 67) of our RA patients complained of pain within one week prior to his or her visit and 79.10% (n = 53) of these patients with pain demonstrated positive result on at least one objective sensory testing, signifying high percentage of possible neuropathic pain among rheumatoid arthritic patients. However, disease duration does not correlate well with occurrence of neuropathic pain.

From the 2006 National Institute on Disability and Rehabilitation Research (NIDRR) Spinal Cord Injury (SCI) Measures Meeting, evidence-based review for clinical practice on pain evaluation suggested that cotton wool and high-threshold von Frey filament to be applied on testing for mechanical allodynia and hyper/hypoalgesia, respectively [13]. Von Frey filaments are relatively expensive (Somedic of Sweden offers one set of von Frey filaments at roughly US$ 650) and are not used in most clinical settings here in Taiwan. On the contrary, a 23G needle mounted inside a syringe barrel may be used to detect hyper/hypoalgesia in most clinical practice, and it is readily available [4].

Absence of gold standard on diagnosis of neuropathic pain has hampered its sequential development of effective treatment and evaluation. A group of specialists made up of neurologists, scientists, neurophysiologists and neurosurgeons established a task force and revised IASP definition on neuropathic pain after intensive review of the literature and frequent consensus conferencing; a grading system composed of four criteria for neuropathic pain was proposed [14]. Another Italian group performed a prospective study collecting 124 patients with sensory neuropathy from a referred number of 486 patients for evaluation; spontaneous remission of neuropathic pain occurred in 10.9% of patients with small fiber neuropathy while 30.4% of patients experienced further deterioration [15]. Only after consensus on the definition and diagnosis of neuropathic
pain becomes available, will scientific research progress and uncover the neuropathology of such a complex condition; then more effective treatment be provided to our patients.

Our study is limited by its small size and lack of prospective follow-up of each patient’s condition. Additionally, assumption of allodynia and/or altered pinprick threshold to be pathognomonic of neuropathic pain may oversimplify this complex and challenging disease. More sophisticated study design enrolling larger numbers of patients are needed for better understanding of neuropathic pain among patients, thus better care can be provided for them.

References

神經性疼痛在類風濕性關節炎的盛行率

鍾德正  歐燦騰  顏正賢  林育志  劉宏文  蔡文展
高雄醫學大學附設醫院  迷素免疫風濕科

目的：研究在類風濕性關節炎病人中，發生神經性疼痛的比例；同時，也調查罹病時間長短和發生神經性疼痛的關係。方法：將葛魯蘋教授翻譯的Brief Pain Inventory（BPI，原作者Dr. Cleeland）以問卷調查的方式在南部某醫學中心過敏免疫風濕科門診調查類風濕性關節炎病人的神經性疼痛盛行率；感覺神經測試也一併記錄在問卷中。病人之發炎指數紅血球沈降速率（ESR）和C-反應蛋白（CRP）也記錄在問卷中，以研究這兩者之間是否有相關。問卷調查時間自2008年三月起至六月底止。結果：一百位符合1987年美國風濕病學院類風濕性關節炎診斷標準的病人接受問卷調查；其中25人因資料不足而排除。75個病人資料進行統計。其中以女性病人佔多數（62位女性，84%），平均年齡為55.64歲，平均罹病時間為11.08年，近九成病人（67/75，89.33%）陳述在求診前一週內出現疼痛情形。在這65位病人，以0為“不痛”到10為“這輩子沒這麼痛過”的疼痛指數量表，他們最痛的疼痛指數平均為5.74分（範圍從1分到10分），最輕微的疼痛平均為1.78分（範圍從0分到9分），過去一週大部分時間的疼痛指數為3.54分（範圍從0分到10分）。在67位有陳述疼痛病人，他們的平均罹病時間是11.19年；其中40位（59.70%）病人出現allodynia，47位（70.15%）病人出現altered pinprick threshold。結論：文獻指出allodynia及altered pinprick threshold和神經性疼痛的強烈相關性，在我們類風濕性關節炎合併疼痛的病人中出現神經性疼痛的比例達79.10% (53/67)。然而，罹病時間的長短和神經性疼痛的表現並沒有正相關。

關鍵詞：神經性疼痛，類風濕性關節炎，allodynia，altered pinprick threshold