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Relationship Between Pain and Neuropathic Symptoms in Chronic Musculoskeletal Pain

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ABSTRACT

Objective. The present study aimed to assess neuropathic symptoms, their stability over time and relationship to pain intensity, pain distribution, and emotional distress in patients with musculoskeletal disorders.

Design. This is a prospective study.

Setting. The study was done at the Department of Physical Medicine and Rehabilitation at Ulleval University Hospital.

Patients. Eighty-six subjects between 18 years and 70 years with chronic musculoskeletal pain participated. Forty-nine subjects had widespread pain and 39 subjects fulfilled the American College of Rheumatology (ACR) criteria for fibromyalgia.

Outcome Measures. McGill pain drawing, pain intensity (visual analog scales), emotional distress (Hopkins Symptom Checklist v 25), and fibromyalgia impact questionnaire were the recorded predictors, and neuropathic symptoms (Leeds assessment of neuropathic symptoms and signs—LANSS) were the main outcome variable which was assessed over 4 months.

Results. The mean LANSS score was 6.7 (standard deviation 5.6). Thirteen percent of the subjects had a score of 12 or more. Self-reported LANSS symptoms did not change over the 4 months follow-up, and the reliability of measurements as evaluated by intraclass correlation coefficient was 0.78. In a backward multiple regression analysis, the presence of fibromyalgia diagnosis and emotional distress remained the final predictors for neuropathic symptoms.

Conclusions. Our study demonstrates that neuropathic symptoms are prominent features of chronic musculoskeletal pain and are stable over time. These symptoms were closely related to emotional distress and to the diagnosis of fibromyalgia. The results lend support to the theory that neuropathic symptoms represent an underlying sensitization.

Key Words. Pain; Muscle; Neuropathic Symptoms; LANSS

Introduction

Chronic pain is generally regarded as having either a nociceptive or a neuropathic genesis [1], but the exact mechanisms are still debated. The main symptom of chronic musculoskeletal disorders is pain. These conditions are additionally characterized by a wide variety of health complaints and, often, elements of emotional distress [2].

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The recent work by Treede et al. define neuropathic pain as a direct consequence of a lesion or disease affecting the somatosensory system, in order to distinguish neuropathic dysfunction from physiologic neuroplasticity [3]. In musculoskeletal disorders, a cluster of symptoms are reported, which partly overlap with the symptoms associated to nerve damage [4,5]. In the majority of these disorders, the causes of symptoms are assumed to be nociceptive [6,7]. Hence, there is no clear relationship between the pain mechanisms, pain experience, and clinical findings [8,9]. This is illustrated by the results of Fishbain et al. [10],

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reporting that fibromyalgia patients score above the cutoff for neuropathic pain. Damage to the somatosensory system is not documented in fibromyalgia [5], which leads to the question if there are other mechanisms behind the neuropathic symptoms accompanying pain in musculoskeletal disorders.

Muscles are suggested to be the most frequent source of the pain in musculoskeletal disorders [11]. The nociceptive afferents, as well as the dorsal horn neurons signaling pain from the muscles, are susceptible to sensitization [12]. The attributes of sensitization are hyperalgesia, but sensitization also implies that innocent mechanical stimuli like touch, muscle contractions, and thermal stimuli are experienced as painful. A high percentage of patients with chronic pain show hyperalgesia, which is enhanced responses to noxious stimulation [13,14]. Sensitization is suggested to be the mechanism behind this increased response and is also of importance for development of chronic pain [15].

Up to 50% of the population is affected when chronic pain is defined as pain or discomfort in one or more sites for at least 3 months [7]. In the chronic situation, multiple pain sites are much more common than pain in only one body area [16], and having pain in one location increases the tendency to develop pain in other body areas [17]. This pattern may represent a general sensitization, and it would therefore be expected that the pain distribution was associated with the neuropathic symptoms. If pain intensity reflects hyperalgesia, one would also expect a relationship between pain intensity and neuropathic symptoms.

Several risk factors have been identified regarding the development of chronic pain [18,19]. Among the strongest predictors is emotional distress, including depression [20]. Depression is more frequent in patients with musculoskeletal pain, and is reported at higher levels in the chronic compared with the acute situation [21] and in the presence of generalized compared with localized pain [22]. More widespread pain distribution is also associated to impaired function and disability [16], which need to be taken into consideration when investigating the relationship to neuropathic symptoms.

Another important question is how stable neuropathic symptoms are over time in patients with musculoskeletal pain conditions. It is well known that pain intensity varies within and over days, whereas the distribution of pain is a more stable feature [23]. The associated health complaints vary substantially with time [24], whereas the time pattern of neuropathic symptoms is not documented.

The main aims of the present study were to assess neuropathic symptoms in patients with localized and generalized musculoskeletal disorders, and if pain and emotional distress were associated to the level of neuropathic symptoms. Second, we wanted to assess the stability of these symptoms over time.

Material and Methods

Subjects

Ninety-eight subjects recruited from Oslo University Hospital Ulleval, Department of Physical Medicine and Rehabilitation and from the Norwegian Fibromyalgia Association were included in the study. The inclusion criteria were age between 18 years and 70 years, tender muscles on palpation either localized or generalized, and musculoskeletal pain for more than 3 months. The exclusion criteria were history or clinical signs of nerve injury or disorder, surgery during the investigation period, inflammatory rheumatic disorders, and painful medical conditions apart from the musculoskeletal system. All subjects gave their written informed consent to participation, and the study was approved by the Regional Ethics Committee of Medical Research in Norway.

Procedure

All the subjects underwent a clinical examination, including examination for the American College of Rheumatology (ACR) criteria for fibromyalgia [25] and muscle tenderness. In addition to muscle tenderness, subacromial impingement or frozen shoulder was common in subjects with shoulder pain. Disc generation and spondylosis were common among the subjects with neck and low back pain. At inclusion, sociodemographic data and current pain status were registered. The pain drawing from the McGill Pain Questionnaire, the Leeds assessment of neuropathic symptoms and signs (LANSS), the Fibromyalgia Impact Questionnaire (FIQ), and the Hopkins Symptom Checklist 25 (HSCL-25) were completed at baseline. Pain intensity and painful body areas were registered. All the questionnaires refer to symptoms and signs during the last week.

The participants filled in questionnaires including pain intensity, painful body areas, and a short version of the LANSS on the first week of the

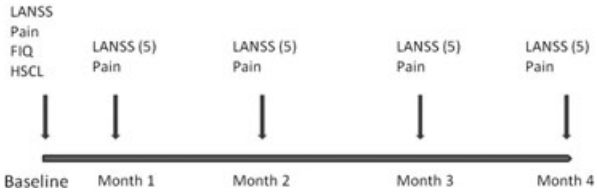

Figure 1 Measurements at baseline and follow-up in the study. Full version of LANSS was used at baseline and five-item LANSS (5) at the first weeks of the following 4 months. FIQ = Fibromyalgia Impact Questionnaire; HSCL = Hopkins Symptom Checklist; LANSS = Leeds assessment of neuropathic symptoms and signs.

month for 4 months (Figure 1). The questionnaires were returned by post the day after each registration.

Measures

Pain intensity was recorded on 100-mm visual analog scales (VAS) with end points "no pain" and "worst possible pain." The subjects were asked to rate the "usual" pain intensity, and the pain intensity during exercise during the previous week on two separate VAS. The wording was: "Indicate by making a mark along the scale below the intensity of the painful sensation at its usual intensity during the last seven days" [26], and "How intense was your pain during exercise during the last seven days? Set a mark on the scale for usual intensity." Exercise was defined as physical leisure activity.

Painful body areas were shaded on the McGill pain drawing, depicting the front and the back of a human body, and the number of painful body areas was counted (range 0–50) [27].

The LANSS [28] was developed to assess the clinical signs of neuropathic pain, and to identify patients in whom the pain experience was dominated by neuropathic mechanisms. The LANSS was translated into Norwegian following accepted procedures [29]. The questionnaire contains five items comprising questions of thermal and dysesthesia qualities, evoked pain, paroxysmal pain, and autonomic dysfunction, and two items requiring testing for allodynia and pin prick threshold. The item responses are weighted and the sum score ranges from 0 to 24. A score of 12 or more is the cutoff applied regarding diagnosing a neuropathic pain disorder. At the time the study started, the S-LANSS [30], which is a self-report questionnaire of the LANSS, was not available. Hence, the first five items in LANSS were used for the self-reported follow-ups over the 4 months. These five items give a maximum score of 16.

The FIQ [31] contains 19 items. Ten items contain the dimension of functioning in the last week, and are scored on a four-level Likert scale from 0 = always to 3 = never. These items are summed in a score termed FIQf, with a range from 0 to 30. One item in FIQ represents depression (FIQd) and validated by Burckhart et al. [31]. FIQd is scored on a 100-mm VAS with end points "not depressed" and "very depressed." The question is "How depressed or blue have you felt?"

The HSCL-25 [32] assesses emotional distress. A Norwegian translation was used [33]. It is scored on a four-level Likert scale ranging from not at all "1" to very much "4," and contains 25 items. The scores of the items are summed and then divided by 25. A mean symptom score of 1.75 or more has been reported to be a good predictor of current help seeking [33], and is often used as cutoff. Subscale scores can also be calculated for the three dimensions of HSCL-25: anxiety, depression, and somatization.

Statistics

The Statistical Package for Social Sciences (SPSS 14.0, SPSS Inc., Chicago, IL) was used for the analyses. Parametric methods and nonparametric methods were used according to the distribution of data. HSCL-25 scores and its subscales were skewed, hence log10 transformed data were used in the analysis, and the data presented with median and interquartile range (IR). Association between the different parts of LANSS were analyzed by Pearson correlation analysis. Backward multiple regressions were performed with LANSS as the dependent variable, and age and gender, duration of pain, usual pain intensity, pain during exercise, number of painful body areas, FIQf, FIQd, and log HSCL-25 as independent factors. Independent factors with Pearson correlation coefficients above 0.7 were not entered in the same regression analysis. Hence, number of painful body areas was taken out when diagnostic category (fibromyalgia or not) was included in the analysis. Changes in the self-reported LANSS scores from baseline to the fourth month were assessed by repeated measures analysis of variance. HuynH-Feldt corrected F and P values are reported. Change in usual pain intensity was included in the analysis as a covariate, and the interaction effect was analyzed. Stability of the self-reported LANSS and the five items contained from baseline to the fourth month were analyzed by two-way mixed intraclass correlation coefficients (ICC [2,1]) [34]. The magnitude of the

individual variations is also evaluated by coefficient of variation (CV).

Results

Subjects and Clinical Characteristics

Eighty-six of the 98 included subjects completed the registrations over 4 months. The 86 participating subjects were similar to the 12 dropouts regarding age, gender, education, physical exercise, and level of emotional distress ($P > 0.18$) (Table 1).

Forty-nine subjects had widespread pain. Of these, 39 subjects fulfilled the ACR criteria for fibromyalgia. Another 10 subjects had pain distributed bilaterally and both in the upper and lower part of the body. One subject had pain in the left side of the body. The remaining 36 subjects had localized pain, including neck pain (N = 5), low back pain (N = 10), and shoulder pain (N = 21).

Pain, Function, and Emotional Distress

Average usual pain intensity over the last 7 days was 43 mm (standard deviation [SD] 18). Average pain during exercise was 40 mm (SD 27). The mean number of painful body areas was 17 (SD 13), ranging from 4 to 38.

Problems in daily functioning (FIQf) had a mean score of 10 (SD 7), which indicates that the subjects had problems with daily activities most of the time. FIQd had a mean score of 24 (SD 25) (median 15, IR 41). Emotional distress represented by the HSCL-25 score was median 1.7 (IR 0.6). The scores for the HSCL-25 subscales were highest for somatization with a median of 2.00 (IR 1.14), followed by depression 1.56 (IR 0.67), and anxiety 1.44 (IR 0.64) ($P < 0.02$).

LANSS Scores in Different Diagnostic Groups

Mean LANSS score was 6.9 (SD 5.7). Thirteen percent of the subjects had a score of 12 or more.

Table 1 Characteristics of participants and dropouts

	Dropouts (N = 12)	Participants (N = 86)
Age (years), mean (SD) (IR)	44 (12)	48 (12)
Females (N)	67%	83%
Pain duration (years), mean (SD)	10(10)	12(10)
Educational level (N)		
<13 years, vocational	67%	55%
>13 years, academic	33%	45%
Full/part-time employment (%)	42	49
Sick leave/disability pension (%)	58	51
No regular exercise (%)	58	65
Regular exercise (%)	42	35

IR = interquartile range; SD = standard deviation.

Table 2 LANSS score (mean and SD) and number of subjects with LANSS scores above 12 according to the diagnostic groups (N = 86)

Diagnostic Groups	LANSS Score	LANSS >12 (N)
Generalized pain (N = 10)	3.8 (4.8)	1
Fibromyalgia (N = 39)	9.5 (5.4)	10
Low back pain (N = 10)	5.4 (4.3)	0
Neck pain (N = 5)	7.0 (6.9)	1
Shoulder pain (N = 21)	4.3 (5.1)	1
Pain half side of body (N = 1)	0	0

LANSS = Leeds assessment of neuropathic symptoms and signs; SD = standard deviation.

LANSS differed among diagnostic groups (Table 2). Patients with fibromyalgia had significantly higher LANSS scores than the other diagnostic groups ($P < 0.03$), except compared with patients with neck pain ($P = 0.35$). Neck pain was not significantly different from low back pain or shoulder pain ($P > 0.34$), but the number of subjects with neck pain was low, hence, statistical comparison should be interpreted with caution.

The frequency of the sensory problems at baseline varied from 9% of the subjects reporting allodynia during clinical examination to 47% reporting hypersensitivity to touch at baseline. Fibromyalgia patients and the other diagnostic groups reported the same pattern of symptoms, but the frequencies were higher in patients with fibromyalgia (Figure 2). The five self-reported items in LANSS were significantly associated with the two items representing signs. However, it is important to note that odd sensations were reported with a higher frequency than assessment of allodynia (Figure 2).

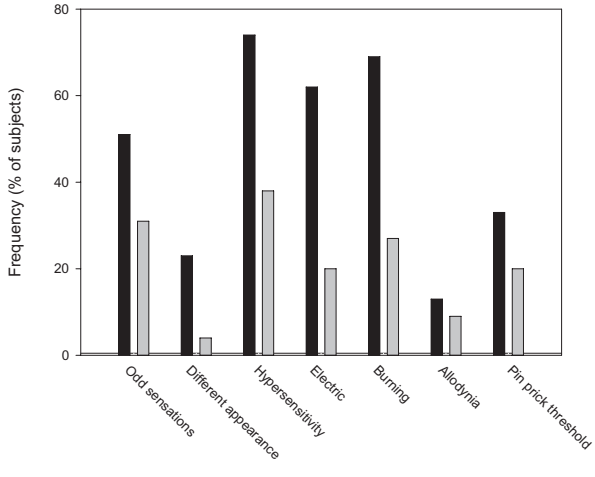

Figure 2 Reported symptoms and responses to examination in LANSS at baseline for fibromyalgia patients (black bars) and the other diagnostic groups (gray bars).

Table 3 Regression analysis

	B	CI B	*P*	Adjusted B	CI Adjusted B	Adjusted *P*
Age	–0.03	–0.12 to 0.08	0.63			
Gender	–2.67	–5.78 to 0.44	0.09			
Duration of pain	0.14	0.02 to 0.26	0.03			
Pain usual	0.09	0.03 to 0.15	0.01			
Pain exercise	0.05	0.01 to 0.10	0.04			
FIQ function	0.3	0.13 to 0.48	0.01			
FIQ depression	0.08	0.03 to 0.13	0.01			
Diagnosis	4.85	2.62 to 7.09	<0.01	3.24	0.52–5.97	0.02
HSCL-25	44.33	30.06 to 58.60	<0.01	37.78	19.28–56.29	<0.001

For diagnosis and HSCL-25, *P* values for adjusted B in the final model are provided.
CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; HSCL = Hopkins Symptom Checklist.

Factors Associated to Neuropathic Symptoms in LANSS

The number of painful body areas and the diagnostic category were strongly correlated ($r = 0.76$, $P < 0.001$) and had to be entered in separate regressions. Hence, the first backward multiple regression analysis was performed with LANSS as the dependent variable and the independent factors pain duration, gender, age, usual pain intensity, pain during exercise, number of painful body areas, FIQf, FIQd, and log 10 HSCL-25 were entered. Only HSCL-25 remained significant (B = 30, confidence interval 19–41, $P < 0.001$) in the final model, explaining 32% of the variance in the analysis. In the second backward multiple regression analysis, the presence of fibromyalgia or not was included as an independent factor instead of the number of painful body areas. The final model explained 39% of the variance with HSCL-25, and the diagnosis of fibromyalgia being statistically significant predictors (Table 3). When each factor was entered separately, all factors except age and gender influenced the LANSS score significantly (Table 3).

LANSS, Individual Variations, and Stability over 4 Months

The LANSS self-reported part had a mean score of 5.6 (SD 4.6), which was stable over the 4-month period at the group level, $F(2.6, 195) = 1.50$, $P = 0.21$. The individual variations were, however, large, with a mean CV of 46% (SD 53%). Higher self-reported LANSS scores were associated with higher variability with respect to absolute values over the 4 months, as reflected by a positive correlation between the individuals' mean and SD ($r = 0.30$, $P = 0.009$). ICC (2,1) for single measures of the sum scores of the five self-reported items in LANSS was 0.78. ICC (2,1) for the individual items ranged from 0.58 to 0.71, with the question regarding altered appearance of the painful area having the lowest and the altered sensation to touch having the highest ICC.

No significant changes were found in the four self-reported items in LANSS over the 4 months of registrations ($F[2.7, 195] = 1.50$, $P = 0.22$). Usual pain intensity declined by 6.9 mm (SD 19) ($P = 0.02$) over this period, but no interaction between LANSS and the decline in pain intensity was found ($F[2.70, 178] = 1.32$, $P = 0.27$).

Discussion

Neuropathic symptoms seem to be a prominent feature of chronic musculoskeletal pain. Thirteen percent of the present patients had scores in LANSS above the cutoff for neuropathic pain, despite no history or clinical signs indicating nerve injury. The neuropathic symptoms were associated with more widespread pain localization, and predicted by emotional distress and the diagnosis of fibromyalgia. The neuropathic symptoms did not change significantly over the 4 months registrations even though the pain level declined slightly.

LANSS score above 12 is suggested as a cutoff for high likelihood of a neuropathic pain condition. The frequency of subjects with scores above the cutoff was higher in the present study than reported by Torrance et al. [7] for persons with chronic pain in the general population. This discrepancy may be explained by the high number of patients with fibromyalgia participating in our study. None of the subjects in the present study had any history or clinical signs of nerve injury except the sensory symptoms and signs reported in LANSS. The question is, then, which mechanisms cause the neuropathic symptoms in musculoskeletal disorders and what is the relationship to the mechanisms behind the pain? In a study by Jensen et al., reduced vibrotactile sense was found in

subjects reporting pain in the arm related to prolonged computer use [35]. The interpretation of this study was that repetitive motions could cause nerve compression and associated pain. However, changes in sensory perception may equally well represent a sensitization process [2], and be related to altered central processing of the signals [36]. High LANSS scores were associated to duration of pain, usual pain intensity, pain intensity during exercise, as well as functioning, and depression. Age and gender did not affect the LANSS scores. However, when including all factors in the analysis, the main predictor was emotional distress, and the number of painful body areas was not included in the final model. Widespread pain was, of course, strongly associated to the diagnosis of fibromyalgia. Interestingly, when substituting widespread pain by the diagnosis of fibromyalgia or not, diagnostic entity added to emotional distress as a unique predictor in the final model. This model also explained more of the variance. The present results are in agreement with Fishbain et al., also reporting neuropathic symptoms in fibromyalgia patients [10].

Pain intensity did not contribute to the final model. The interpretation of this result may be that pain intensity plays a more important part in the acute situation, whereas chronic pain is modified by several factors, masking the relationship to hyperalgesia and other neuropathic symptoms. Reduced function, as evaluated by FIQ, was associated with a higher number of neuropathic symptoms in the present study, but outweighed by emotional distress and the diagnosis of fibromyalgia. The present patients reported elevated levels of emotional distress, and the most prominent feature was somatization. Cutoff of the subscales in HSCL-25 has, to our knowledge, not been reported and validated, but depression was reported at a significantly lower level than somatization. We also evaluated depression by FIQ, which had a sufficiently low correlation to emotional distress to be included in the analysis. No separate contribution of this factor was found. The major predictor of neuropathic symptoms in the present study was emotional distress. Emotional distress is a well-known predictor of chronic pain [20] and is related to sensory changes and altered nociceptive processing [4]. Sensory symptoms adding to pain are associated with poor recovery [37]. In order to plan effective intervention, it is important to establish a cause–effect relationship between emotional distress and the sensitization process, and to clarify the mechanisms involved.

Recent research lends support to peripheral and central mechanisms of sensitization being important in the spread of pain and developing chronic pain [38–40]. This is in line with studies reporting sensitization as an important mechanism in the development of fibromyalgia [38].

Our study was conducted before the S-LANSS had been introduced and validated [30]. We used the full version of LANSS at inclusion and the five self-reported items of LANSS for the repeated measurements over the 4 months. These five items are similar to the items in S-LANSS. The present study was designed to shed light on the symptom profile, and LANSS was not used to identify possible neuropathic conditions.

In the present study, the neuropathic symptoms did not change significantly over time. Furthermore, the reliability of the sum score of the five LANSS items was good, as evaluated by the ICC. This is in accordance with previous results indicating acceptable reliability for LANSS and S-LANSS [28,30]. To our knowledge, the stability of the individual items over time has not been investigated previously. Analyzing single items of the LANSS, the highest reliability was found for self-reported altered sensation to touch. A discrepancy was found in the frequency of altered touch sensation and allodynia during clinical examination. The meaning of these items may be different, but it could be of significance to investigate whether this discrepancy is also present in patients with verified nerve damage.

Conclusion

Our study demonstrates that neuropathic symptoms are prominent features of chronic musculoskeletal pain and are stable over time. The symptoms were closely related to emotional distress and to the diagnosis of fibromyalgia. The results lend support to the theory that these symptoms represent an underlying sensitization. Prospective studies may elucidate this hypothesis. Attention to the emotional factors is needed in treatment of patients with musculoskeletal pain and associated neuropathic symptoms.

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