Психо-емоційні аспекти формування характеристик больових синдромів у хворих на розсіяний склероз

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Актуальність. Больові синдроми, тривога і депресія є поширеними синдромами при розсіяному склерозі (РС). Коморбідність болю і депресії чи болю і тривоги існує приблизно у однієї третини хворих на РС. На основі біопсихосоціальної моделі болю, враховуючи високу поширеність цих симптомів та часте їх поєднання при РС, яке є значно частішим, ніж у загальній популяції, можна припустити зв'язок між характеристиками болю та тривожністю і депресією у хворих на РС.

Мета. Оцінити поширеність тривоги та депресії серед хворих на РС з больовими синдромами та проаналізувати зв'язок тривоги та депресії з характеристиками больових синдромів у хворих на РС.

Методи. Дані були зібрані проспективно у Львівському обласному центрі розсіяного склерозу. Обстежено 120 випадково відібраних пацієнтів з підтвердженим діагнозом розсіяний склероз. У 104 з них протягом останнього місяця були больові синдроми. Зібрано скарги та анамнез, проведено аналіз медичної документації, неврологічний та загальний медичний огляд пацієнтів. Симптоми депресії та тривоги оцінювали у всіх пацієнтів за допомогою шкали госпітальної тривоги та депресії (HADS). У пацієнтів із больовими синдромами, для оцінки характеристик болю, використовували Візуальну аналогову шкалу (VAS), Коротку форму больового опитувальника МакГілла-2 (SF-MPQ-2), Pain Detect.

Результати. Рівні тривоги та депресії були вищими в групі хворих на РС з болем. Рівень тривоги становив 9,0 [6,0; 12,75] у групі з болем і 7,0 [4,0; 9,25] у групі без болю (р=0,04). Рівень депресії становив 7,0 [4,0; 10,0] у групі з болем і 4,0 [1,75; 6,0] у групі без болю (р<0,01). Встановлено, що частка хворих на РС з больовими синдромами та тривогою становила 36,5%, а 29,8% мали субклінічний рівень тривоги; частка хворих на РС з больовими синдромами та депресією становила 19,23%. Частка пацієнтів із тривогою була найвищою серед пацієнтів із нейропатичним болем: 56,3 % ± 8,8 % проти 22,4 % ± 6,0 % при ноцицептивному, р<0,01. Подібна ситуація спостерігається у хворих з депресією. Частка пацієнтів з депресією була вищою в групі з нейропатичним болем 37,5% ± 8,6%, порівняно з 14,3% ± 5,0% при ноцицептивному, р=0,02. Частка хворих на РС без ознак тривоги та депресії достовірно вища серед пацієнтів із ноцицептивним болем (р<0,05). Також встановлено кореляційний зв'язок рівнів тривоги тривоги та депресії з рівнем прояву нейропатичного компоненту болю (r=0,40; p<0,01 та r=0,30; p<0,01). Рівні тривоги та депресії корелювали із середньою інтенсивністю болю за місяць (r = 0,21; p=0,03) і не мали статистично значущого зв'язку з інтенсивністю болю на момент обстеження та найсильнішим болем за останній місяць. Тривога та депресія мали кореляційні зв'язки з усіма компонентами структури больових синдромів (за даними SF-MPQ-2), але найбільш виражений прямий кореляційний зв'язок виявлено між тривогою та афективним компонентом болю (r=0,57; p<0, 01). Також виявлено, що рівень тривоги вищий у пацієнтів з 2-3 больовими синдромами, ніж у пацієнтів з одним больовим синдромом: 12,0 [8,0; 14,0] балів проти 8,0 [5,0; 11,0] балів, р<0,01. Крім того, локалізація болю в руках, плечах і спині була пов'язана з більш високим рівнем тривоги (r=0,22; p=0,03).

Висновки. Больові синдроми, тривожність та депресія широко поширені серед хворих на РС, і між ними існує взаємозв'язок. Хворі на РС з болем, мають вищий рівень тривоги та депресії, ніж хворі на РС без болю. Примітно також, що серед хворих на РС з больовими синдромами виявляється високий рівень тривоги. Тривога та депресія мають виражений зв'язок з нейропатичним компонентом болю у хворих на РС. Крім того, наявність більш ніж одного больового синдрому, висока середня інтенсивність болю за місяць, пов'язані з більш високими рівнями тривоги та депресії. Локалізація болю в руках, плечах і спині пов'язана з більш високим рівнем тривоги. Ці відкриття в поєднанні з сучасними нейровізуалізаційними технологіями, використаними на наступному етапі нашого дослідження, дозволять краще зрозуміти біль та його структуру, а також тривогу і депресію.

Ключові слова: розсіяний склероз, біль, тривога, депресія, нейропатичний.

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Psycho-emotional aspects in the formation of pain syndrome characteristics in patients with multiple sclerosis

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Introduction. Pain syndromes, anxiety, and depression are common syndromes in multiple sclerosis (MS). Comorbidity of pain and depression or pain and anxiety exists in up to one-third of MS patients. Based on the biopsychosocial model of pain, given the high prevalence of these symptoms and their frequent combination in MS, which is significantly higher than in the general population, we can hypothesize the relationship between the characteristics of pain and anxiety and depression in patients with MS.

Objectives. To assess the prevalence of anxiety and depression among MS patients with pain syndromes and analyze the relationship between anxiety and depression with pain syndromes' characteristics in patients with MS.

Methods. Data were collected prospectively at Lviv Regional Multiple Sclerosis Center. 120 randomly selected patients with a confirmed diagnosis of multiple sclerosis were examined. 104 of them had pain syndromes during the last month. Complaints and medical history, analysis of medical records, neurological and general medical examination of the patients were collected. Depressive symptoms and anxiety were assessed in all patients using the Hospital Anxiety and Depression Scale (HADS) questionnaire. In patients with pain syndromes, the Visual analogue scale (VAS), Short-form McGill Pain Questionnaire 2 (SF-MPQ-2), Pain Detect were used to assess pain characteristics.

Results. The levels of anxiety and depression were higher in the group of MS patients with pain. The level of anxiety was 9.0 [6,0; 12,75] in the group with pain and 7.0 [4,0; 9,25] in the group without pain (p=0.04). The level of depression was 7.0 [4,0; 10,0] in the group with pain and 4.0 [1,75; 6,0] in the group without pain (p<0,01). It was found that part of MS patients with pain syndromes with anxiety was 36.5%, and 29.8% had a subclinical level of anxiety; part of

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MS patients with pain syndromes with depression was 19.23%. The proportion of patients with anxiety was highest in patients with neuropathic pain: $56.3\% \pm 8.8\%$ vs. $22.4\% \pm 6.0\%$ with nociceptive, $p<0.01$. A similar situation is observed in patients with depression. The share of patients with depression was higher in the group with neuropathic pain $37.5\% \pm 8.6\%$, compared to $14.3\% \pm 5.0\%$ with nociceptive, $p=0.02$. The proportion of patients with MS without signs of anxiety and depression is significantly higher among patients with nociceptive pain ($p<0,05$). Also, the correlational relationship between the level of anxiety and depression with the level of the neuropathic type of pain manifestation was found ($r=0,40$; $p<0,01$ and $r=0,30$; $p<0,01$). Levels of anxiety and depression correlated with the average pain intensity per month ($r = 0,21$; $p=0,03$) and did not have a statistically significant relationship with pain intensity at the time of examination and the strongest pain for the last month. The anxiety and depression had correlations with all components of the structure of pain syndromes (according to sfMPQ-2), but the most pronounced direct correlation was found between anxiety and the affective component of pain ($r=0,57$; $p<0,01$). It was also found that the level of anxiety was proved to be higher in patients who have 2-3 pain syndromes, than in patients with one pain syndrome: 12.0 [8,0; 14,0] points against 8.0 [5,0; 11,0] points, $p<0.01$. Besides, this localization of pain in the arms, shoulders and back was related to higher levels of anxiety ($r=0.22$; $p=0.03$).

Conclusion. Pain syndromes, anxiety, and depression are widespread among patients with MS and there is a relationship between them. MS patients with pain have higher levels of anxiety and depression than MS patients without pain. It is also noteworthy that among MS patients with pain syndromes, high levels of anxiety are detected. Anxiety and depression also have a pronounced relationship with a neuropathic component of pain in patients with MS. Besides this, the presence of more than one pain syndrome, high average pain intensity per month is associated with higher levels of anxiety and depression. The localization of pain in the arms, shoulders and back is related to higher anxiety levels. These discoveries, combined with modern neuroimaging technologies used in the next step of our study, will provide a better understanding of both pain and its structure, as well as anxiety and depression.

Keywords: multiple sclerosis, pain, anxiety, depression, neuropathic.

Introduction

In July 2020, the International Association for the Study of Pain (IASP) announced a revised Definition of Pain. According to it, pain is an unpleasant emotional and sensory experience associated with or resembling the one associated with actual or potential tissue damage (1). IASP expanded this definition by adding six key notes, which allowed revealing the term meaning better. These notes develop the understanding of such a phenomenon as pain, demonstrating that pain is not just nociception but a subjective feeling of the patient based on previous experience and related to psychological and social factors. The patient can express their pain not just in words, and the doctor should respect the experience of pain described by the patient.

This newly revised definition and key notes emphasize the importance of pain assessment in the biopsychosocial model of pain, which was first conceptualized in 1977 by George Engel, suggesting that to understand a person's medical condition, it is not simply biological factors to consider, but also social and psychological aspects (2). Since then, this concept is gaining popularity, especially in case of chronic pain, and new research data expand the evidence base of this concept.

Multiple sclerosis (MS) is a progressive degenerative disease of the central nervous system characterized by disseminated foci of demyelination, responsible for the diverse clinical picture of MS. The symptoms of MS vary considerably from patient to patient (3,4). Among them, one of the most common symptoms is pain syndrome. According to meta-analysis, 63% of MS patients have pain syndromes. However, in some studies, especially those published in recent years, these figures reach 90% (5–8). Depression and anxiety are also common in case of MS

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and are manifested more as compared to the general population. Also, the prevalence of clinically significant depressive or anxiety symptoms is higher in case of MS as compared to other diseases. According to a recent meta-analysis, pooled mean prevalence of depression in MS patients is 30.5%, and 22.1% of MS patients suffer from anxiety (9).

Some studies have shown that every third patient with MS has comorbidity of pain syndromes and anxiety or pain syndromes and depression (6,9). Given the high prevalence of these symptoms and their frequent combination in case of MS, which is significantly higher than among the general population, we can hypothesize the relationship between the characteristics of pain, anxiety and depression. Nevertheless, it is not easy to determine the vector of this relationship because both anxiety and depression can affect a patient's subjective feeling of pain. On the other hand, pain can be one of the reasons which affect anxiety and depression. The improved understanding of these relationships will increase the effectiveness of diagnostics and therapeutic methods in terms of the personalized approach to patient care, taking into account their psycho-emotional and social characteristics. The aim of study was to assess the prevalence of anxiety and depression among MS patients with pain syndromes and analyze the relationship between anxiety and depression and pain syndrome characteristics in patients with MS.

Methods
Data were collected prospectively at Lviv Regional Multiple Sclerosis Center during 2019-2020. The sample was randomly formed of patients with a confirmed diagnosis of multiple sclerosis according to 2017 MacDonald criteria, who were treated at Lviv Regional Multiple Sclerosis Center. One hundred twenty patients met the inclusion/exclusion criteria and were included in the study. One hundred four of them had pain syndromes during the past month. After obtaining written informed consent for the participation in the study, a collection of complaints and medical history, analysis of medical records, neurological and general medical examination of the patients was performed.

Depressive symptoms and anxiety were assessed in all patients using the Hospital Anxiety and Depression Scale (HADS). This scale is divided into two groups of questions, associated with anxiety and depression, with 7 questions in each. Based on the patient's responses, a numerical value was formed, where the higher number is associated with higher levels of depression and anxiety (10).

For patients with pain syndromes, to assess pain syndrome characteristics, standardized questionnaires were used: the visual analogue scale for pain (VAS), Pain Detect, short-form McGill Pain Questionnaire 2 (sfMPQ-2).

Statistical processing of the obtained results was performed with the help of standard methods using the application package MS Excel, RStudio v. 1.1.442, and R Commander v. 2.4-4. The analysis was performed according to the median (Me) and 25% (Q1), and 75% of the quartiles (Q3), which is appropriate for the non-Gaussian distribution of indicators in the variation range. The significance of the difference in groups was assessed based on the nonparametric Mann-Whitney (U) criterion for independent populations. Spearman's correlation analysis was performed to evaluate the relationships between indicators. Data at $p<0.05$ was considered probable.

Criteria for inclusion in the study were multiple sclerosis confirmed using the 2017 MacDonald criteria, aged 18 or older, patient's personal written consent for the participation in the study.

Exclusion criteria included severe concomitant congenital and acquired diseases, other serious neurological diseases in the anamnesis.

The study was approved by Danylo Halytsky Lviv National Medical University's Ethical Committee. The permission of the Bioethics Commission to conduct research was obtained: No. 1 dated January 21, 2019. MS patients were extensively informed about the aims and procedures of the investigation and signed informed consent forms.

Results
104 of 120 patients with MS had pain syndromes during the last month, which is 86,67%. When comparing groups of MS patients with and without pain syndromes, no statistically

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significant difference was found between these groups in the disease duration, the number of relapses, and EDSS score. However, a statistically significant difference was found between groups in the levels of anxiety and depression. Levels of anxiety and depression were higher in the group of MS patients with pain. The level of anxiety was 9.0 [6.0; 12.75] in the group with pain and 7.0 [4.0; 9.25] in the group without pain (p=0,04).   The level of depression was 7.0 [4,0; 10,0] in the group with pain and 4.0 [1.75; 6.0] in the group without pain (p<0.01).

The next important step was a detailed study of the psycho-emotional characteristics of MS patients with pain. The median age in the sample of MS patients with pain was 38.0 [31.8; 47.0], including 76 women and 28 men. The disease duration in the sample was from 0 to 31 years old, the median – 6.0 years old [3.0; 12.25]. The median EDSS score was 3.5 [3.0; 4.0]. The median number of MS relapses before the examination in the history of patients was 10,0 [3.0; 15.0].

We found that pain characteristics and severity were not strongly correlated with the duration of the disease, the number of relapses and the EDSS score (11,12). Therefore, we primarily focused on studying the relationship between the characteristics of pain and anxiety and depression.

When assessing the level of anxiety, the median level of anxiety was 9.0 [6.0; 12.75] (fig.1). A score of 9 on the HADS scale corresponds to a subclinical level of anxiety, which starts with 8 points, which indicates that probably a significant number of MS patients with pain syndromes have subclinical and clinical levels of anxiety.
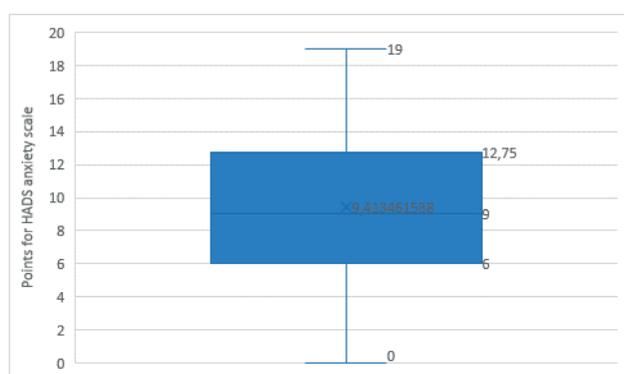
To assess the structure of anxiety in MS patients with pain, patients were divided into groups according to the level of anxiety. It was found that part of MS patients with pain syndromes and anxiety was 36.5%, and 29.8% had a subclinical level of anxiety (fig.2). Such a high level of comorbidity of pain syndromes and anxiety indicates their potential relationship.
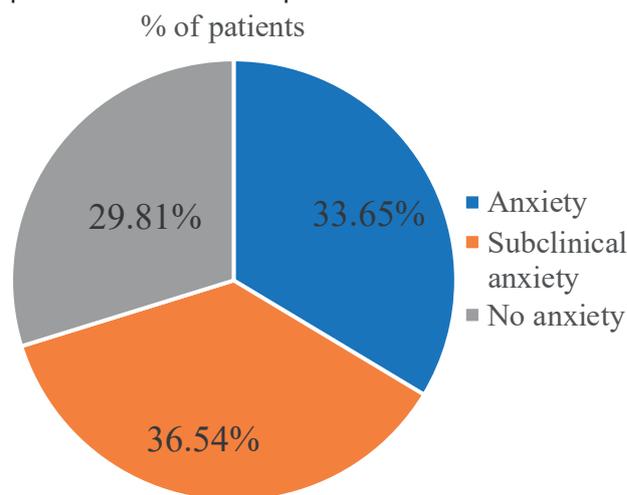
Figure 2. The structure of anxiety level among patients with MS with pain

When assessing the level of depression in MS patients with pain, the median level of depression was 7.0 [4.0; 10.0] (fig.3). A median score of 7 on the HADS scale corresponds to the absence of depression, but it borderlines with a subclinical level of depression, which indicates that probably a significant number of MS patients with pain syndromes do not have a clinical level of depression. However, they may have some symptoms of depression.
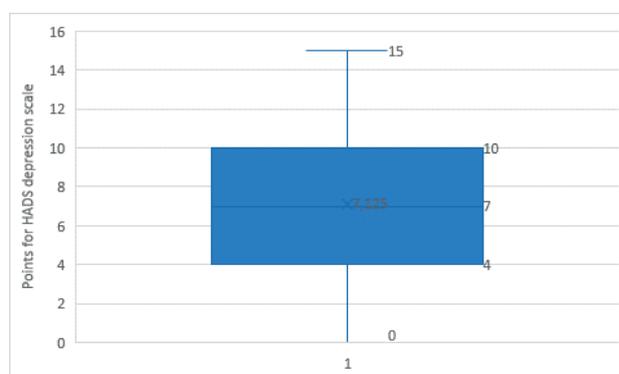

Figure 1. The level of anxiety among MS patients with pain

Figure 3. The level of depression among MS patients with pain

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Table 1

Distribution of patients by level of anxiety and depression in groups with different types of pain syndromes (%)

Indicators	Neuropathic		Nociceptive		indeterminate		p		
	n	$P \pm m_p$	n	$P \pm m_p$	n	$P \pm m_p$	1 з 2	1 з 3	2 з 3
Anxiety									
0-7 (No anxiety)	6	18.8±6.9	24	49.0±7.1	5	21.7±8.6	0.01	0.78	0.03
8-10 (subclinical level of anxiety)	8	25±7.7	14	28.6±6.5	9	39.1±10.2	0.72	0.26	0.37
11 and more (anxiety)	18	56.3±8.8	11	22.4±6.0	9	39.1±10.2	<0.01	0.21	0.14
Depression									
0-7 (No depression)	10	31.3±8.2	32	65.3±6.8	15	65.2±9.9	<0.01	0.01	0.99
8-10 (subclinical level of depression)	10	31.3±8.2	10	20.4±5.8	7	30.4±9.6	0.27	0.95	0.35
11 and more (depression)	12	37.5±8.6	7	14.3±5.0	1	4.3±4.3	0.02	<0.01	0.21

To assess the structure of depression in MS patients with pain, patients were divided into groups according to the level of depression. It was found that part of MS patients with pain syndromes and depression was 19.23%, and more than half of patients did not have depression (fig.4).
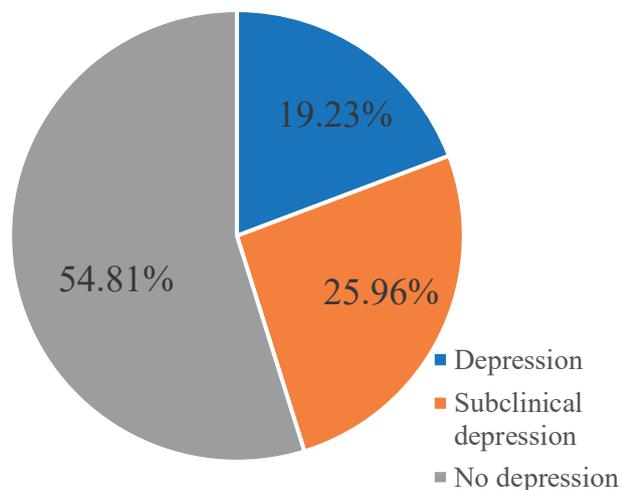

Figure 4. The structure of the level of depression among MS patients with pain

The next step was to evaluate the relationship of anxiety and depression levels with the characteristics of pain syndromes structure by the type of pain. According to the results obtained from the Pain Detect questionnaire, patients were divided into groups with the neuropathic, nociceptive and indeterminate types of pain. Median values of anxiety and depression were higher in patients with neuropathic pain com-

pared to nociceptive type: 11.5 [9.0; 15.3] points against 8.0 [5.0; 10.0] points (p<0.01) for anxiety and 9.5 [6.0; 12.0] points against 6.0 [3.0; 9.0] points (p=0.01) for depression. Patients were divided into groups according to the type of pain and the level of anxiety and depression. This distribution is presented in table 1.

As can be seen in Table 1, the share of patients with anxiety was the highest among patients with neuropathic pain 56.3% ± 8.8% vs. 22.4% ± 6.0% with nociceptive, p<0.01. A similar situation is observed for patients with depression. The proportion of patients with depression was higher in the group with neuropathic pain 37.5% ± 8.6%, as compared to 14.3% ± 5.9% with nociceptive pain, p=0.02. The share of MS patients without signs of anxiety and depression is significantly higher among patients with nociceptive pain (p<0,05).

This gave us a reason to analyze the correlation between anxiety and depression and the neuropathic type of pain. Visualizations of the correlation between anxiety and depression and the neuropathic type of pain are presented in Figures 5 and 6.

As can be seen in Figures 5 and 6, the correlations between anxiety and depression and the manifestation of the neuropathic type of pain are r=0.40; p<0.01 and r=0.30; p<0.01, respectively, which demonstrates the presence of a direct correlational relationship of moderate strength between the level of anxiety and

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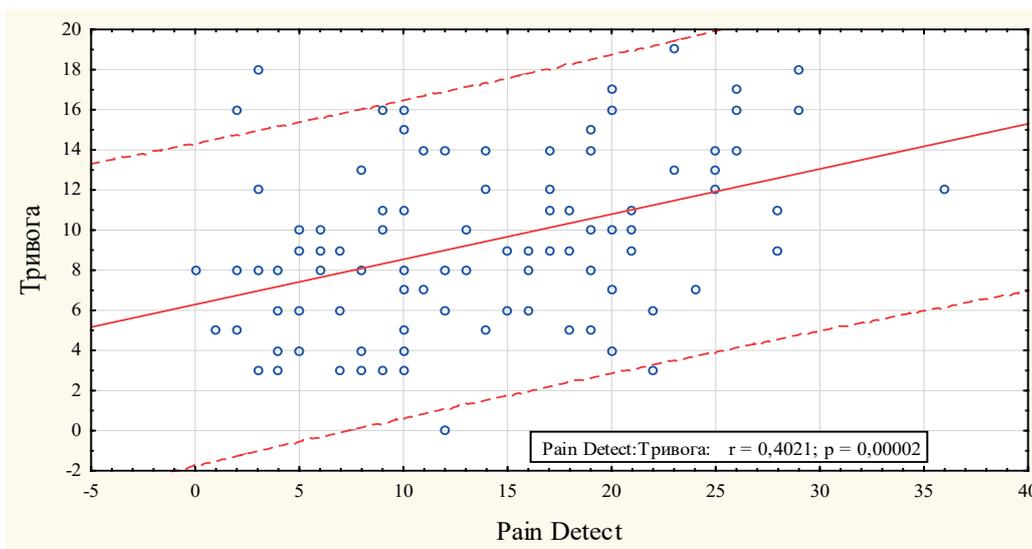Original research: Clinical sciences

Figure 5. The correlation between the level of neuropathic pain component
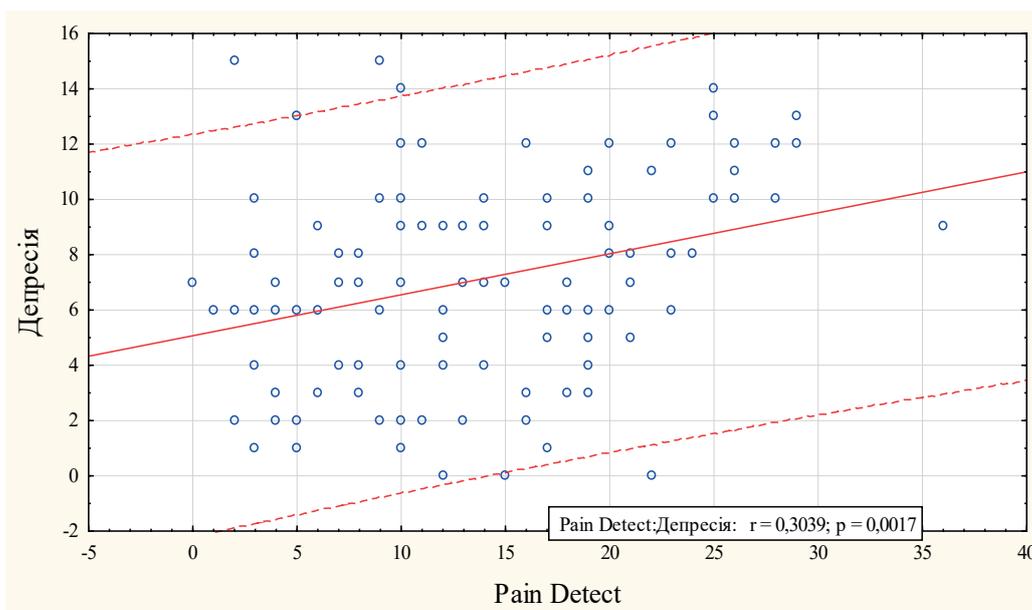(based on Pain Detect score) and the level of anxiety

Figure 6. The correlation between the level of neuropathic pain component
(based on Pain Detect score) and the level of depression

depression (HADS scores) and the level of the neuropathic type of pain manifestation (based on the score of the PainDetect questionnaire).

It is also essential to assess whether pain patterns are related to the levels of anxiety and depression. For this purpose, MS patients with pain syndromes were divided into groups according to 4 typical pain syndrome patterns. Typical pain syndrome course patterns are the following: pattern 1 – prolonged pain with nearly identical intensity; pattern 2 – constant low-intensity pain with periodic high-intensity attacks; pattern 3 – attacks of pain, without pain in between attacks; pattern 4 – constant paroxysmal pain. The results of anxiety and depression analysis in patients with different typical course patterns showed that the level of anxiety did not differ significantly in patients from these groups, but the level of depression was higher in patients with a typical pattern 4 (constant paroxysmal pain): 9.0 [5.0; 12.0]

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Table 2

Data on correlations between the level of anxiety and depression and pain indicators of the SF-MPQ-2 questionnaire

Indicators of pain	Anxiety		Depression	
	r	p	r	p
SF-MPQ-2	0.51	<0.01	0.38	<0.01
Prolonged	0.46	<0.01	0.34	<0.01
Sharp	0.38	<0.01	0.26	0.01
Affective	0.57	<0.01	0.40	<0.01
Neuropathic	0.37	<0.01	0.34	<0.01

Table 3

The correlation between manifestations of anxiety, depression and the characteristics of intensity, localization of pain

Indicators	Anxiety		Depression	
	r	p	r	p
Pain intensity now	0.08	0.39	0.11	0.28
The strongest pain intensity in a month	0.13	0.17	0.17	0.08
Average pain intensity per month	0.21	0.03	0.20	0.03
Localization of pain				
Head	0.11	0.26	0.05	0.58
Shoulders, back	0.22	0.03	0.10	0.29
Legs	0.09	0.36	0.19	0.05
Hands	0.22	0.03	0.11	0.25

points (p=0.03 with pattern 3). The share of patients with clinically severe depression was the highest (2.0-4.4 times) in the group of MS patients with a typical pattern 4 – 35.3 ± 8.2% (p=0.02 with pattern 3). The relationship between higher levels of depression and pattern 4 is also confirmed by the presence of a direct correlation between them (r = 0.20; p=0.04). In other patterns, no proven difference between the levels of depression in the groups was found.

To better understand the impact of anxiety and depression on the pain syndrome structure, we used the SF-MPQ-2 questionnaire, which demonstrates the levels of 4 main indicators of pain (prolonged, sharp, affective, neuropathic). The results of the correlation analysis between indicators of anxiety and depression and components of the structure of pain are presented in Table 2.

Analyzing the data presented in Table 2, we see a significant correlation between anxiety and depression and all components of the structure of pain syndromes. The most pronounced direct correlation was observed between anxiety and depression and the affective component of pain: r = 0.57, p <0.01 with anxiety, r = 0.40, p = <0.01 with depression. This proves that with increasing levels of anxiety and depression in MS patients, the level of long-term, sharp, affective and neuropathic components of pain increases, affecting the growth of the affective component of pain.

Important characteristics of pain are intensity and localization. Data on the relationship of anxiety and depression with the characteristics of their intensity (based on VAS scores) and localization of pain are presented in Table 3.

As can be seen in Table 3, the levels of anxiety and depression are correlated with the average pain intensity per month (r = 0.21, p=0.03; r = 0.20, p=0.03) and do not have a statistically significant relationship with pain intensity at the time of examination and the strongest pain for the last month. When assessing the relationship between pain localization and the levels of anxiety and depression, we see in Table 3 that the localization of pain in the arms, shoulders and back is directly related to higher levels of anxiety (p=0.03).

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It was also found that the level of anxiety was proved to be higher in patients who have 2 to 3 pain syndromes than in patients with one pain syndrome: 12.0 [8.0; 14.0] points against 8.0 [5.0; 11.0] points, p <0.01. Accordingly, the share of patients in the group with 2 to 3 pain syndromes with clinically pronounced anxiety was 2.1 times higher than in patients with one pain syndrome: 53.8 ± 8.0% vs. 26.2 ± 5.5%, p<0.01. The level of depression did not differ significantly in patients in these groups (p> 0.05). Therefore, patients with 2 to 3 pain syndromes have higher levels of anxiety than patients with 1 type of pain, which may be related to the shaping of pain memory associated with the previous experience of pain.

Discussion
The prevalence of pain among MS patients, which we observed in our study, correlates with the prevalence obtained in the studies conducted in other Eastern European countries and is even slightly higher than in neighboring Poland and Lithuania (6,7). Studies in Western Europe and the United States report a lower prevalence of pain in MS patients, which may be related to the study design. However, given this frequency of pain syndromes among patients with MS, pain should be considered in more detail, especially in terms of psycho-emotional and social factors (8,13).

Like other researchers who have dealt with this topic, we understand that it is not easy to assess the relationship between anxiety and pain or depression and pain, given its versatility (14,15). However, our study demonstrated its existence and certain features of its characteristics. Depression has previously been considered a risk factor that can be modified to improve the quality of pain treatment in patients with MS and pain syndromes in case of other diseases (13,16). At the same time, most studies pay less attention to anxiety. Amtmann et al. proposed a model with indirect effects of pain on depression. They showed that the effect of chronic pain on depression was almost entirely mediated by fatigue, anxiety, and sleep disturbance. More severe pain was associated with more significant fatigue, anxiety, and sleep disturbance, which in turn were associated with higher levels of depression (17). Our study found an association between the presence of pain syndromes and both higher levels of anxiety and depression. At the same time, we found a higher prevalence of anxiety than depression among MS patients with pain.

In a recently published Lithuanian study where MS patients were compared with a control group, higher anxiety and depression levels were more common among MS patients than among the control group regardless of their experience of pain. However, when comparing patients without pain between the groups, no difference was found. Therefore, it may suggest that multiple factors cause higher anxiety and depression levels in the group of MS patients, and pain can be one of the important ones (7).

In the previously published studies, attempts were made to find links between anxiety, depression and pain in MS patients. However, these relationships were mainly assessed by comparing MS patients with and without pain, but insufficient attention was paid to pain characteristics. The study of Scherder et al. showed that depression and anxiety predict both pain intensity and pain effect but did not research other characteristics of pain and the relationship with the type of pain (18). Our study results expand this understanding by demonstrating that anxiety and depression are associated with the average intensity of pain per month rather than the most intense pain in the course of the month or pain at the time of examination. Regarding components of pain, we have expanded the understanding of the relationship by demonstrating associations between the levels of anxiety and depression and all components of pain, most pronounced with the affective component.

An important finding of this study is the direct correlation of the levels of anxiety and depression with the neuropathic type of pain and the much higher prevalence of anxiety and depression in patients with neuropathic pain than with nociceptive pain. Another interesting finding is that patients with 2 to 3 pain syndromes, experience higher anxiety levels than patients with one pain syndrome. We also found that MS patients with constant paroxysmal pain experienced higher levels of depression, and the localization of pain in the arms, shoulders and back is directly related to higher anxiety levels.

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In conclusions, pain syndromes, anxiety, and depression are widespread among patients with MS and there is a relationship between them. MS patients with pain have higher levels of anxiety and depression than MS patients without pain. It is also noteworthy that high levels of anxiety were identified in MS patients with pain syndromes. Anxiety and depression also have a pronounced relationship with a neuropathic component of pain in patients with MS. Besides this, the presence of more than one pain syndrome, high average pain intensity per month are associated with higher levels of anxiety and depression. The localization of pain in the arms, shoulders and back is related to higher anxiety levels. These discoveries, combined with modern neuroimaging technologies used as the next step of our study, will provide a better understanding of both pain and its structure, as well as anxiety and depression.

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